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JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY

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ELECTRO-ENCEPHALOGRAPHY IN CASES OF SUB-CORTICAL TUMOUR

BY

W. GREY WALTER and V. J. DOVEY

From the Burden Neurological Institute, Bristol

(RECEIVED 23RD MAY, 1944)

THE application of electro-encephalography to organic brain lesions has mainly been limited to the study of cases with involvement of the convexity of the hemispheres. In these an expanding lesion is usually associated with potential changes at a frequency well below the normal range—1 to 3 c/s. It is generally accepted that discharges at this frequency are pathological when their amplitude approaches that of the normal rhythms (20μV). When localized by multi-channel recording, even lower potentials indicate cortical abnormality. These low frequency or " delta " rhythms (Walter, 1936, 1937, 1938) are not specifically diagnostic of new growth for they are also seen in traumatic and degenerative conditions, and in idiopathic epilepsy.

One of the main difficulties in interpreting abnormal e.e.g. records is that the waveform is rarely simple or repetitive, as in the electro-cardiogram. Many observers have remarked that in cases of new growth, the waveform of the slow potential changes is particularly irregular and complex, whereas in cases of idiophathic epilepsy the discharge tends to be more stereotyped and rhythmic. An irregular and complex waveform is hard for the unaided eye to interpret, and it is also likely to contain many components. The e.e.g. is simply a graph of voltage difference against time. The interpretation of such a graph depends upon the capacity of the eye and brain to analyse a sinuous line in a conventional co-ordinate system. Most people understand readily the meaning of a simple curve, and a little practice gives facility in appreciating a simple periodic one, such as a sine curve. When, however, a periodic curve contains several components, appreciation is more difficult and when the periodicity is irregular and the components variable, the efficiency of the direct visual analysis falls off and fatigue quickly sets in. Now in the case of the e.e.g. a simple periodic curve is an extreme rarity, for only occasionally are two consecutive waves exactly similar, and in the more common complex records the eye invariably compromises by attending only to those components which possess the greatest regularity and amplitude. It is this tendency which has led to the designation of certain basic rhythms such as the " alpha " and " delta " rhythms and thus to an over-simplification of the whole subject.

Various ways of supplementing primary inspection have been devised. Most are tedious and many are unreliable. The only principle which can be of value is to break the record up into segments and to analyse each segment into its component parts, as a prism displays the colour content of white light. This implies a mathematical wave analysis of a particularly clumsy type, but fortunately the computations can be made quite accurately by machinery. The first useful analyser for the e.e.g. was described by Grass and Gibbs (1938), and this has been used by the Boston workers for some years with good results. It has the disadvantages that a special photographic record must be made as well as the usual ink-traced one, that the analysis is not available until the photo-record has been processed and run through the analyser, and that the analysis curve cannot be immediately referred to the primary trace to which it applies. In order to produce an analysis without these hindrances, another type of instrument has been built. A technical description of it has appeared elsewhere (Walter, 1943*a* and *b*), and the details of design need not be gone over here.

Method

The apparatus traces a frequency histogram or band spectrum over the primary record. For this purpose an arbitrary epoch of ten seconds has been chosen to which each spectrum analysis applies. The analysis is performed automatically every ten seconds, and is traced over its primary record in the natural order of frequencies. In the first model the frequencies included were 2, 3, 4, 5,

6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22 c/s. ; in a later model the range was extended to include in addition 1·5, 2·5, and 24, 27, 30 c/s. An arbitrary ordinate scale is used, corresponding approximately to (average—amplitude × duration) of oscillation at each of the frequencies during the ten-second epoch. Thus a 10 c/s. oscillation with an average amplitude during the epoch of half the possible maximum, lasting throughout the epoch, would be represented as a kick of the analyser pen of half the maximum at the 10 c/s. point in the frequency scale. An oscillation of maximum possible size, but lasting for only half the epoch would be represented by a kick of the same size. When oscillations at several frequencies are present simultaneously, all will be shown as kicks at the appropriate point on the frequency scale, each kick indicating the amount of " activity " at that frequency during that epoch.

To a first approximation the amplitude of any given oscillation in the e.e.g. is an indication of the number of neurones engaged in synchronous electrical activity at that frequency. The analyser kick, therefore, shows the temporal and spatial extent of electrical activity at any or all of the frequencies covered in the area of the brain from which the record was taken, during a ten-second epoch. Its great advantage over the unaided eye is that it is not deceived nor discouraged by the presence of a small intermittent rhythm close in frequency to a large regular one. Since the spectrum is traced directly over the primary record, the analytic summary may be used to attract attention to features of the primary record which would otherwise be overlooked, and an essential feature of the new technique is that the primary and spectral records are used to complement one another, and the combined data are immediately available to direct further recording or experiment.

It has been found that the introduction of this form of analysis extends the range and interest of the whole subject, a survey of which is in course of preparation. Advances have already been made in problems relating to diagnosis and neurophysiology. The complexity of records from cases of cerebral tumour was the first subject to be clarified. Analysis of these records shows that the irregular form of delta waves is due to the presence of components which are quite steady in their mean frequency, but very variable in their amplitude. It was found in the course of routine recording from many cerebral tumour cases that usually these other components had a frequency of from 4 to 7 c/s. and that the focus of this activity was often different from that of the slow delta discharges. It seemed probable that the association of these medium frequencies with the new growth was due to a different mechanism from that leading to the slower rhythms. It was suspected that this other mechanism was connected with involvement of the sub-cortical centres and material was gradually collected to check this hypothesis.

Material

Attention was first directed to a group of cases in which the nature and extent of the tumour had been verified either at operation or post mortem. There are 31 cases in this group. This number is too small for formal statistical treatment, and, indeed, less has been learned by this method than by study of each individual case and correlation of details. A much larger number of cases has been studied, but not all have been thoroughly investigated pathologically. In general it was found that all these cases exhibited, among various other features, significant activity in the 4–7 c/s. band. In 21 cases there was good correlation between the superficial location of the 4–7 c/s. rhythm and the deeper effects of the new growth. In two cases the 4–7 c/s. rhythm was posterior and bilateral, and in these the lesion was in the posterior fossa. In eight cases the activity was more diffuse, and in these there were either multiple lesions or a grossly raised intracranial pressure.

Results

Considering the 21 cases in which the location data are trustworthy, these may be divided into :—

1. Those in which the tumour arose superficially and was spreading into or pressing upon the sub-cortical structures (5 cases).
2. Those in which the tumour arose in the deeper structures and was spreading outwards or compressing the cortex (5 cases).
3. Those involving the deeper structures to a much greater extent and affecting the cortex only indirectly (11 cases).

The records from Category 1 all showed a more or less prominent delta rhythm (1–3 c/s.), localized to the area around the superficial involvement of the tumour. In addition they exhibited in varying degrees activity in the 4–7 c/s. band. This was often masked in the primary record by the larger, slower rhythms and usually was wider in focus. In certain cases it arose from areas remote from the superficial aspect of the tumour (Fig. 1A, B, C). Typically, the delta rhythm was at 2 c/s., and the other at 6 c/s. That is, the higher frequency tended to be a multiple or third harmonic of the slower. This explains the delta waves with square or triangular forms. Both of the frequencies vary by about a half c/s. and also fluctuate in amplitude, so that the variety of waveforms is very large.

The records from Category 2 all showed 4–7 c/s. activity which seemed most prominent where the tumour approached the surface. There was in addition a smaller delta rhythm, also indefinitely localized and varying from moment to moment in frequency and amplitude. In these cases the slower rhythms in the primary records tended to be masked by the faster ones (Fig. 2A and B). The 4–7 c/s. activity was often bilateral although its larger amplitude on one side and the co-existence of the delta rhythm usually served to lateralize it. In these cases the abnormal potentials are small, and they are often masked by the normal alpha rhythm of 8–9 c/s., so that in many cases the abnormal component would not have been suspected without analysis. Furthermore the 4–7 c/s. activity tends to show most clearly in the parieto-temporal regions on the more affected side, and careful location technique and analysis were needed to separate the pathological components from the alpha rhythm.

The records in Category 3 are more difficult to classify. In general the more restricted the new growth the less prominent the delta rhythms. The

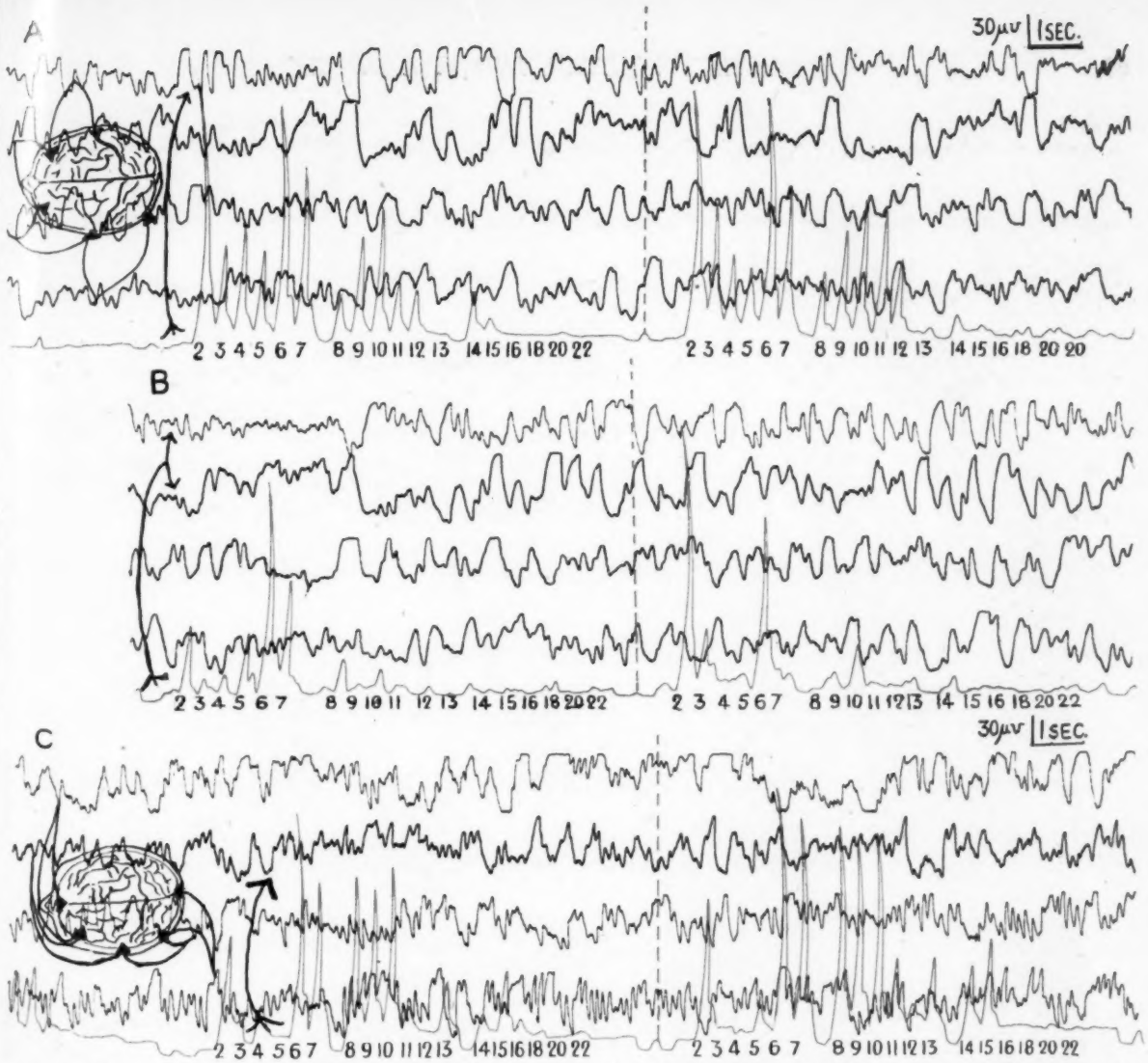


FIG. 1.—(A). e.e.g. from case with tumour shown in Fig. 4. Distribution of rhythms in Fig. 5. (B). The same, using phase discriminating analysis. (C). e.e.g. from case with tumour shown in Fig. 6. Distribution of rhythms in Fig. 7.

For explanation of analysis, see text. The coloured trace is a frequency histogram drawn automatically by the analysing pen. Each kick represents the amount of activity during the ten-second epoch at the frequency indicated by the number at the base of the kick. The small double downward deflections indicate divisions between epochs.

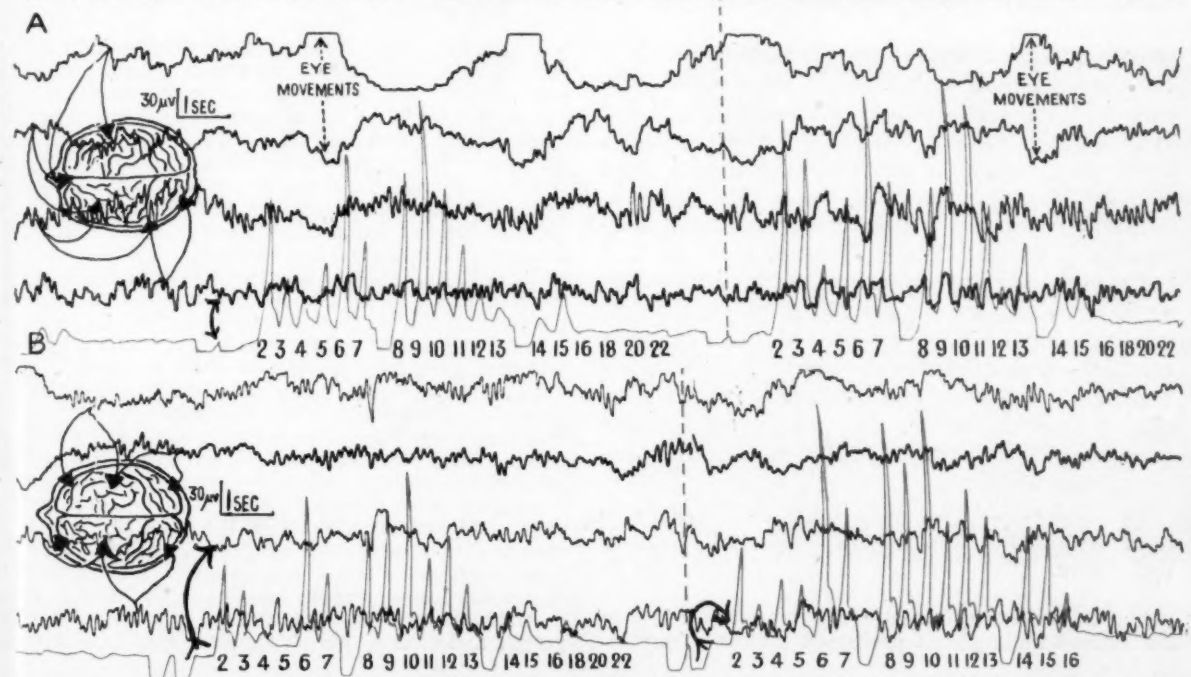


FIG. 2.—(A). e.e.g. from case with tumour shown in Fig. 8 (X-rays) and Fig. 9. Distribution of rhythms in Fig. 10. (B). e.e.g. from case with tumour shown in Fig. 11 (X-rays) and Fig. 12. Distribution of rhythms in Fig. 13.

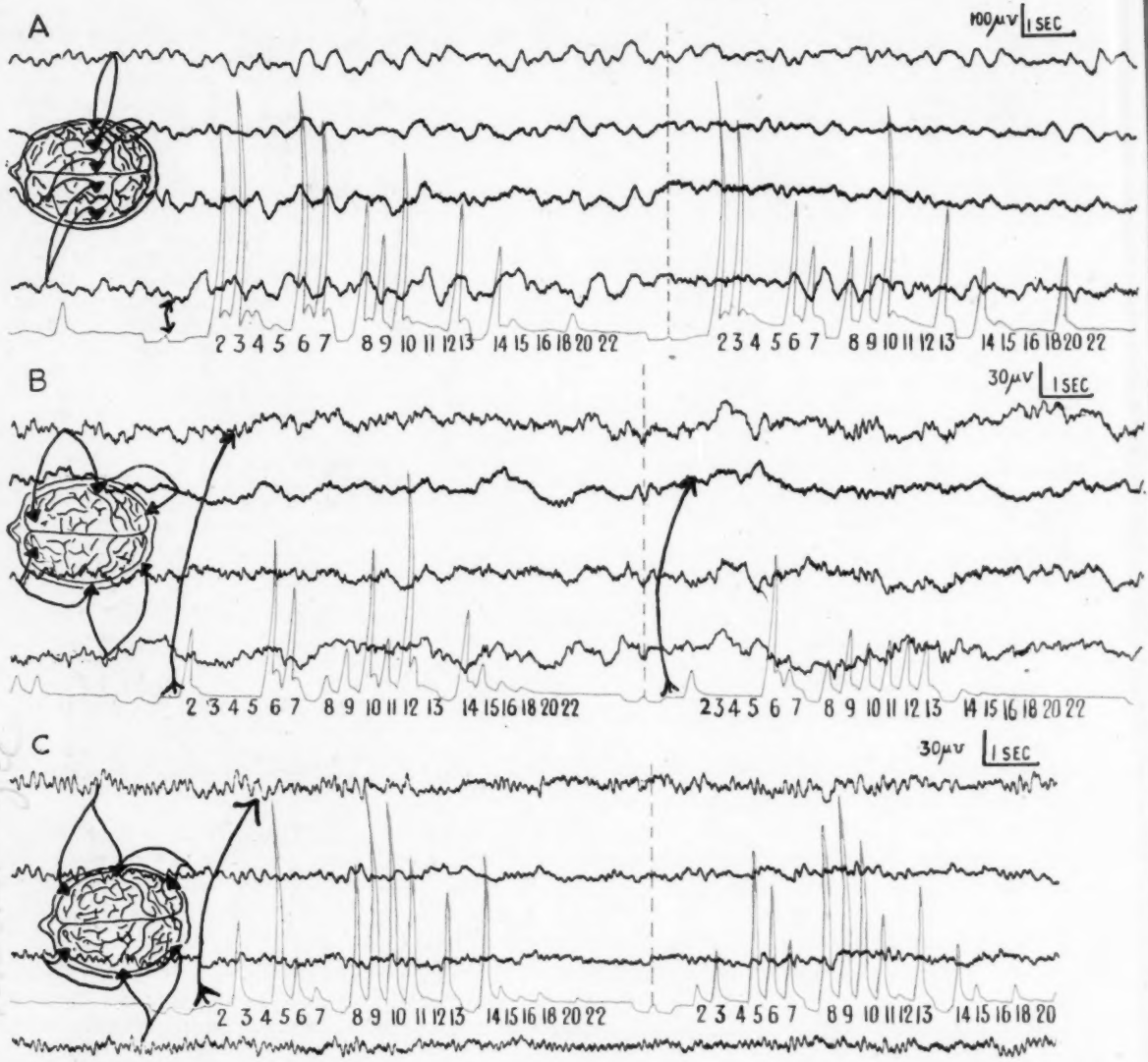


FIG. 3.—(A). e.e.g from case with umour shown in Fig. 14. Distribution of rhythms in Fig. 15. (B). e.e.g. from case of tumour shown in Fig. 16. Distribution of rhythms shown in Fig. 17. (C). e.e.g. from case of tumour shown in Fig. 18. Distribution of rhythms in Fig. 19.

only cases exhibiting any really significant delta activity were those with a raised intracranial pressure (Fig. 3A). In the others the most prominent feature of the records was activity at about 6 c/s. from the post-central and parieto-temporal areas (Fig. 3B, C).

Turning now to the eight cases with more equivocal or complex clinical features, these showed correspondingly more diverse abnormalities in the e.e.g. All had lesions involving the sub-cortical structures, and all the e.e.g.s had one feature in common—activity in the 4–7 c/s. band. This activity was usually bilateral and most prominent in the parieto-temporal areas. It was often of low potential and therefore tended to be masked by the other larger rhythms.

Before discussing this material in general, a more detailed reference to the figures will help to clarify the picture.

Fig. 1A is a record from a patient who complained of headache, vomiting, and prolonged attacks of unconsciousness for four months. Examination indicated a frontal lesion with fluctuating pyramidal signs on both sides. In the record, the dominant components from all areas are at 2 and 6 c/s. There is only a trace of normal alpha rhythm at 10 c/s. There are occasional waves at an even lower frequency than 2 c/s. The slow components frequently show a square or triangular waveform indicating the presence of third harmonics. This corresponds in the analysis to the peaks at 2 and 6 c/s. Location in this case was obviously difficult but was assisted by the method illustrated in Fig. 1B, whereby analysis is made of the components out-of-phase in channels 1 and 2, discriminating against those components which are in-phase in the two channels. In the first epoch the dominant out-of-phase component is at 6 c/s., while in the second epoch, both 2 and 6 c/s. are present. Comparative phase-discriminating analyses of this type were also made between the other channel-pairs. These revealed delta foci in the right frontal and left fronto-temporal regions, suggesting a large space-occupying lesion between these foci, obliterating the cortex and pressing inwards on the basal ganglia. The patient died shortly after operation. At post mortem a meningioma the size of a tangerine was found arising in the left frontal region, pressing both left and right frontal lobes apart, and reaching as far down as the basal ganglia and diencephalic structures. This deep involve-

FIG. 4.—Tumour location topogram of case with e.e.g. in Fig. 1A.

ment was probably responsible for the patient's prolonged attacks of unconsciousness and for the sudden death. Fig. 4 shows the tumour and Fig. 5 the e.e.g. topogram.

Fig. 1C is from a patient complaining of headache and

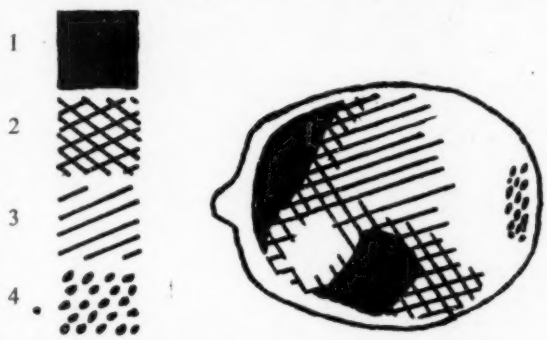


FIG. 5.—e.e.g. rhythm topogram of case with tumour shown in Fig. 4 and record in Fig. 1A.

(1) 1–3 c/s Rhythms [Delta]. (2) 4–7 c/s Rhythms Prominent [Theta]. (3) 4–7 c/s Rhythms [Theta]. (4) 8–13 c/s Rhythms [Alpha].

The shading convention is the same for all e.e.g. topograms (Fig. 7, 10, 13, 15, 17, 19).

loss of vision for a year. The only neurological findings were bilateral optic atophy and astereognosis of the right hand. The record shows an analysis similar to that of Fig. 1A, but there is less activity at the very low frequencies. The dominant feature is the peak at 6 c/s. There is also an irregular but high voltage alpha rhythm. The slow components and the 6 c/s. rhythms both focussed over the left fronto-parietal region. Operation revealed a nodular tumour in this area infiltrating the deeper structures below but not laterally. In this case there was less cortical damage and more localized interference with the basal ganglia than in the patient of Fig. 1A. Fig. 6 shows the tumour and Fig. 7 the e.e.g.

FIG. 6.—Tumour location topogram of case with e.e.g. in Fig. 1C.

topogram. Fig. 2A is from a patient complaining of headaches for several months. The only neurological finding was a doubtful extensor response on the right side. The record again shows a prominent 6 c/s. rhythm localized to the left parietal region and accompanied by a smaller amount of 2–3 c/s. activity. In Fig. 8 are the X-rays showing a calcified mass below the left fronto-parietal region. This was found by biopsy to be an oligodendroglioma. The site of the tumour and

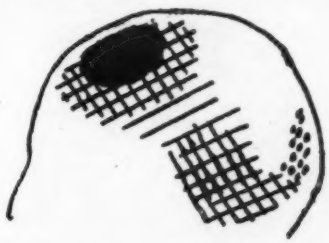


FIG. 7.—e.e.g. rhythm topogram of case with tumour shown in Fig. 6 and record in Fig. 1C.

(1)

(2)

FIG. 8.—X-rays of case with e.e.g. shown in Fig. 2A.

e.e.g. topograms are shown in Fig. 9 and 10. Fig. 2B is from a patient who has had epileptic attacks and headaches for 20 years. Examination showed anosmia and paresis of the left external rectus. The records

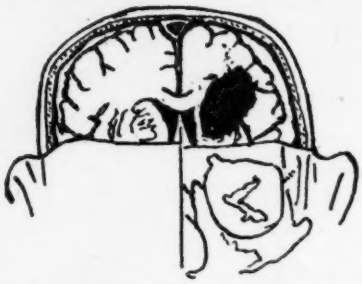


FIG. 9.—Tumour location topogram of case with X-rays shown in Fig. 8 and e.e.g. in Fig. 2A.

show a peak in the 6 c/s. band from the left temporo-parietal leads. The alpha rhythm is normal on the right side with a frequency of 9 c/s. It is present also, though smaller in potential on the left side. The

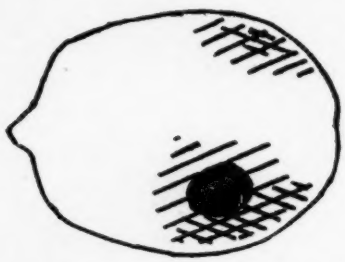
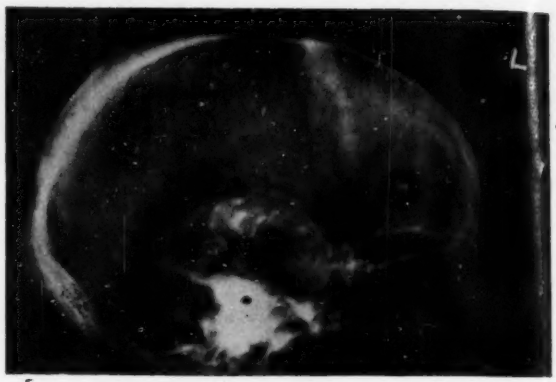


FIG. 10.—e.e.g. rhythm topogram of case with tumour shown in Fig. 8 and 9 and record in Fig. 2A.

activity in the delta bands is much less than in the previous case. The X-rays (Fig. 11) show a sharply defined egg-shaped calcified mass below the left parieto-temporal cortex. The mass location and e.e.g. topograms are shown in Fig. 12 and 13. Fig. 3A is from a patient complaining of headaches and mental deterioration for some weeks. There was a progressive right-sided hemiplegia with a raised intracranial pressure. The records show the widespread slow waves characteristic of raised pressure. On the right side these are smooth and fairly rhythmic and analysis shows few components between 3 and 10 c/s. On the left side the form of the waves is more irregular, triangular or square and analysis shows the presence of components at 6–7 c/s. chiefly from the left parieto-temporal region. Post mortem a metastatic tumour was found involving the left side of the hypothalamus and extending into the posterior fossa. The primary tumour was not found. The site of the tumour and e.e.g. topograms are shown in Fig. 14 and 15. Fig. 3B is from a patient complaining of blurring of vision in the left eye for three years, followed by sudden blindness of both eyes a month before. There was also vomiting and headache and a tendency to general obesity. The vision improved later, leaving a bitemporal hemianopia. The vision of the right eye was better than that of the left. X-rays showed an enlarged and eroded sella turcica. The records show asymmetry of the hemispheres and in the right frontal region the dominant peaks are at 6 and 12 c/s. This is a good example of the value of analysis since the primary trace of channel 1 in this record would be difficult to describe owing to the irregularity and low potential of the discharges. The twelve-cycle rhythm is the second harmonic of the 6 c/s. and is associated with it, the alpha rhythm being a separate component at 10 c/s. of low amplitude. This second harmonic alters the form of the 6 c/s. waves and masks them, tending to a spiky monophasic pattern. Inspection of the primary record shows



(1)

(2)

FIG. 11.—X-rays of case with e.e.g. shown in Fig. 2B.

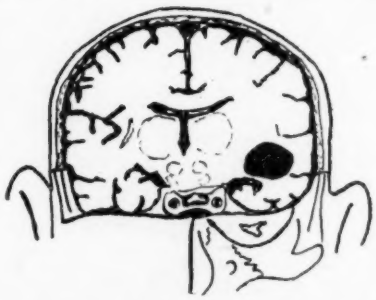


FIG. 12.—Tumour location topogram of case with X-rays shown in Fig. 11 and e.e.g. in Fig. 2B.

FIG. 13.—e.e.g. rhythm topogram of case with tumour shown in Fig. 11 and 12 and record in Fig. 2B.

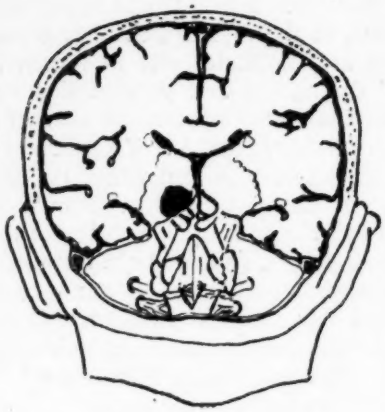


FIG. 14.—Tumour location topogram of case with e.e.g. shown in Fig. 3A.

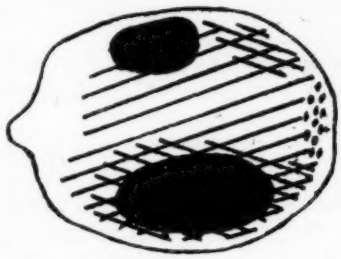


FIG. 15.—e.e.g. rhythm topogram of case with tumour shown in Fig. 14 and record in Fig. 3A.

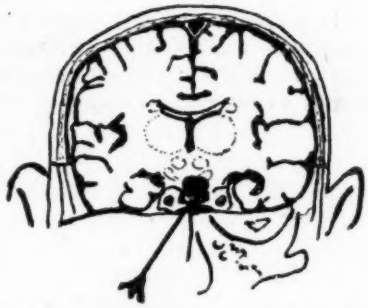


FIG. 16.—Tumour location topogram of case with e.e.g. shown in Fig. 3B.

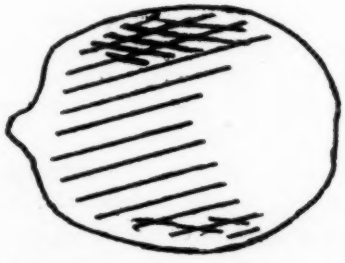


FIG. 17.—e.e.g. rhythm topogram of case with tumour shown in Fig. 16 and record in Fig. 3B.

that the 6 c/s. and 12 c/s. components can occur independently of one another occasionally. This spectrum is abnormal for the frontal lobe and suggests a deep seated lesion. Operation revealed a bulging diaphragma sellæ pressing upon the optic chiasma. A portion of the new growth was removed. Fig. 16 shows the site of the tumour and Fig. 17 the e.e.g. topograms. Fig. 3C is from a patient with a six-months history of headaches, vomiting, vertigo and personality change. There had been a radical amputation of the breast for malignancy two and a half years previously. The only abnormal signs were stupor and engorgement of the retinal vessels.

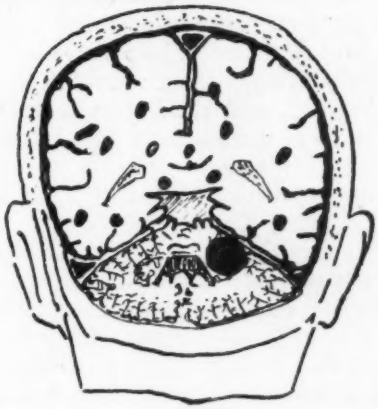


FIG. 18.—Tumour location topogram of case with e.e.g. shown in Fig. 3C.

The records show a prominent peak at 5 c/s. from the right side, focussing over the lower parietal and temporal regions. The alpha rhythm is of normal frequency and focus, though masked in the primary records from the right hemisphere by the slower rhythms. Post mortem

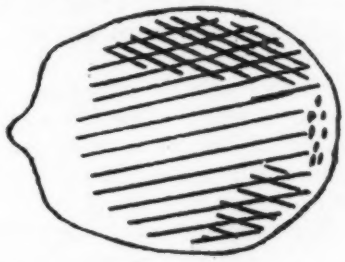


FIG. 19.—e.e.g. rhythm topogram of case with tumour shown in Fig. 18 and record in Fig. 3C.

five months later revealed a metastatic tumour involving the right cerebello-pontine angle with pressure effects in the mesencephalic structures. The tumour location and e.e.g. topogram are shown in Figs. 18 and 19.

Discussion

This detailed description serves to illustrate the way in which electrical activity at about 6 c/s. is associated with involvement of sub-cortical structures. A valid general criticism is that new growth anywhere in the brain is almost certain to affect these structures in some way since they are close to the ventricles and easily damaged by distortion. In most cases of brain tumour these rhythms do exist but in purely cortical lesions they are small and in basal ones they are large. Moreover, in different conditions they appear as a correlate of deep involvement. They are prominent in concussion without gross cortical damage where according to Holbourn (1943), the basal structures bear the brunt of the blow, and in children with behaviour disorders characterized by rage attacks and emotional liability, in whom the 4–6 c/s. waves are particularly large and rhythmic. Similar rhythms have been described by Hill and Watterson (1942) in aggressive

psychopaths. The location of this rhythm in the parietal and temporal regions is also characteristic. In tumours the more affected side shows more of this activity, but a tumour expanding on one side may displace the deeper structures so far to the other side that the disturbance is in effect bilateral.

Some of the material here described was discussed at a meeting of the Electro-encephalographic Society in 1943, and since then at other centres cases of cerebral tumour have been collected which show the 4–7 c/s. activity clearly enough to be seen in the primary record (Gibb and Turner, 1943). In a private report, Cobb (1943) agrees that these frequencies may have significance and suggests that they may " originate in structures adjacent to the third ventricle, more anterior than posterior."

With the analytic method rhythms at many frequencies can be appreciated simultaneously, and as each has its zone of dominance and physiological associations, classification by " cycles per second " becomes clumsy and inadequate. The term " alpha rhythm " is widely known and is clearly more convenient than " rhythm at about 10 c/s. from the occipital region tending to be blocked by visual and mental activity." Similarly " delta rhythm " is shorter than " waves at 1 to 3 c/s. of cortical origin signifying damage, dystrophy or degeneration." In the case of the 4–7 c/s. waves the term which we suggest is " theta."

These waves occur in the state just preceding or following natural sleep. Electrical exploration of normal waking subjects has revealed that with high amplification and phase-discriminating analysis a small peak of energy at 6 c/s. is almost invariable in the parieto-temporal areas, and this peak is augmented when the subject starts to feel remote and is on the verge of drowsiness. In some normal people this peak is large, though never as large as the alpha peak from the occipital region. Sometimes, it is diminished like the alpha rhythm by opening the eyes and mental alertness.

Kennard and Nims (1942) and Kennard (1943) found that in monkeys " lesions of the thalamus alter the pattern of cortical e.e.g.s in general, but most markedly in the post-central areas." These changes were usually the production of waves at 6–8 c/s. as distinct from the normal 8–10 c/s. rhythm, and this effect long outlasted the temporary local changes associated with experimental acute cortical trauma. Lesions of the caudate nucleus and putamen had most effect upon the precentral and frontal areas, while lesions of the thalamus affected most the post-central regions. If, as a working hypothesis, it can be assumed that the 4–7 c/s. oscillations resemble the 8–12 c/s. alpha rhythm in being physiological " rest rhythms," it would be expected that lesions interrupting the transmission of centripetal impulses through the thalamus would tend to augment the 4–7 c/s. activity, much as closing the eyes augments the occipital alpha rhythm. This conception has importance beyond tumour location, since normal maturation of the human nervous system also involves change in the thalamo-cortical relations. Kennard and Nims (1942) have shown that, in the monkey, there is a progressive " increase in amplitude, rate and complexity of pattern " during the first year of life, but closer inspection shows the appearance first of 4–7 c/s. and then of 8–10 c/s. waves. This process is paralleled in human development where the details can be filled in more easily. In human children, analysis of local rhythms shows, even in the infant, activity at 2–3, 5–6, and 8–10 c/s. from the frontal, parieto-temporal and occipital areas respectively. In the first few months the slowest rhythms are dominant, later the medium frequencies, and finally the alpha becomes prominent, but at all times the various frequencies are present in their respective zones. It is not true therefore to say that " the e.e.g. is slower in children than in adults," but it is true that in young children the 4–7 c/s. rhythms are larger in their areas than the 8–12 c/s. are in theirs.

Further evidence that the basal ganglia affect the e.e.g. is given in the report of Gibbs and Gibbs (1941) that complex slow rhythms occur in cases of chorea and athetosis. This is not so, however, in all cases where the basal ganglia are known to be affected, notably in parkinsonism, where the e.e.g. is typically " normal." This discussion serves to emphasize the limits of knowledge of the electrophysiology of the forebrain which results from (1) the difficulty of deciding to what extent a given lesion, experimental or spontaneous is irritative or destructive ; (2) inability to replace removed or damaged nervous tissue to complete an experiment ; (3) The great flexibility of central nervous function leading always to extensive re-routing of impulses and consequent vicarization of function ; (4) the limitations of electrophysiological technique which permit intimate study of one neurone group only if others are sacrificed ; and conversely, in the intact brain reveal only the blurred outline of a possibly irrelevant statistical conglomeration. The last difficulty is in course of solution ; the others are more subtle and more challenging but may be circumvented.

Summary

1. Special automatic analysis and accurate location procedure have been used in the electro-encephalography of cases with cerebral tumours affecting sub-cortical structures.

2. In 31 cases subsequent operation or post-mortem revealed the site and extent of the tumour.

3. In cases with superficial tumours spreading inwards, the site of the tumour exhibited 1–3 c/s. (delta) waves ; the adjacent areas and parieto-temporal regions showed activity at about 6 c/s.

4. In cases with deep tumours spreading outward the main feature was 6 c/s. activity from the cortex above the tumour and/or from the parieto-temporal regions. A small delta rhythm was sometimes seen immediately above the tumour or as a general effect of raised pressure.

5. In cases with deep tumours not affecting the cortex, the 6 c/s. rhythm was the only significant abnormality. This was usually from the parieto-temporal region and often could only be distinguished from the normal alpha rhythm by analysis.

6. In cases with more widespread new growth, the 6 c/s. rhythm was seen whenever the basal structures were affected.

7. The occurrence of rhythms at about 6 c/s. from the parieto-temporal region in these cases is related to the similar rhythms found in other clinical and physiological conditions where the basal structures are involved, and also to the effect of experimental lesions of the basal ganglia in monkeys.

8. It is suggested that rhythms at about 6 c/s. should be termed " theta " rhythms and that such rhythms are characteristic of the resting, immature or isolated parieto-temporal cortex.

We record with pleasure our gratitude to Dr. P. B. Ryan for providing us with the essential anatomical and pathological information accurately and skilfully depicted by Dr. J. E. Fernandes to whom also we are grateful.

References

Cobb, W. A. (1943). Private communication.
Gibb, E. M., and Turner, J. (1943). Private communication.
Gibbs, F. A., and Gibbs, E. L. (1941). *Atlas of Electroencephalography, Cambridge*, U.S.A.
Grass, A. M., and Gibbs, F. A. (1938). *J. Neurophysiol.*, **1**, 521.
Holbourn, A. H. S. (1943). *Lancet*, 245, 438.
Hill, D., and Watterson, D. (1942). *J. Neurol. Psychiat.* **5**, 47.
Kennard, M. A. (1943). *J. Neurophysiol.*, **6**, 233.
—— and Nims, L. F. (1942). *Ibid.*, **5**, 325, 335.
Walter, W. G. (1936). *Lancet*, **2**, 305.
—— (1937). *Proc. roy. Soc. Med.*, **30**, 33.
—— (1938). *J. Neurol. Psychiat*, **1**, 359.
—— (1943*a*). *Electronic Engineering*, June.
—— (1943*b*). *Ibid.*, November.

THE WERNICKE SYNDROME

With Special Reference to Manic Syndromes Associated with Hypothalamic Lesions

BY

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(RECEIVED 12TH JUNE, 1944)

THE following study is based upon five complete cases of Wernicke's syndrome. In only one case was there a history of alcoholism; two of the subjects suffered from pernicious anæmia; one gave a history of hyperemesis gravidarum, and the last of gastric carcinoma. In two further cases, the one of alcoholism and the other of pernicious anæmia, no complete investigation could be carried out; it is known, however, that both these patients had Korsakow's psychosis and in both the mammillary bodies were found to be severely affected.

The occurrence of the Wernicke Syndrome in all these conditions is now a recognized fact (Neubuerger, 1937; Campbell and Biggart, 1939; Sheehan, 1939; Sinclair, 1939; and others). It has also been well established that the common etiological link is a deficiency in thiamine. Alexander (1939, 1940) was able to produce lesions comparable with those of the Wernicke Syndrome in pigeons fed on thiamine-free diet rich in other foodstuffs and containing in excess the vitamins A, the remaining Bs, C, and D. Alexander's results were in accordance with those of Prickett (1934) and Zimmerman (1939/40, 1940), and have since been amplified by similar findings in foxes (Alexander, Green, Evans and Wolf, 1941; Evans, Carlson and Green, 1942) and in cats (Ferraro and Roizin, 1941).

In this paper it is not proposed to describe the pathology of all the cases in detail; this would mean much repetition of findings which have been studied previously. Only one case will be given in full, as it was atypical both clinically and pathologically. The rest of the material will be utilized for comparison and also for the description of certain unusual features which have not been dealt with adequately in previous publications.

Case report *

William H. G., æt. 62, admitted to Cane Hill Hospital on 19th August, 1941. (The following report is by Dr. Lilly, Medical Superintendent.)

Family History: The only abnormality known is that his sister is an inmate of Bexley Hospital. The Medical Superintendent, Dr. L. C. Cook, kindly supplied the following information about her. "She was admitted in 1930 in a very apprehensive, agitated state which soon cleared up, leaving her a simple but stable type of feeble-minded woman, lacking confidence, and incapable of fending for herself independently. She reached standard II at school, but can just read and write. She tells me she got very depressed after her mother died during the last war, but did not have to go to Hospital. I can find no other history of Manic-depressive tendency."

Personal History: Nothing is known of any physical or mental abnormality until the patient's present disease. In March, 1941, he was an out-patient at Charing Cross Hospital suffering from inoperable gastric carcinoma and was sent home to the care of his wife. His psychotic condition commenced at the beginning of July, 1941, when he became elated, giving away expensive presents, and, when remonstrated with by his wife, "flew into a rage," making it impossible for her to take care of him. During the time in St. Francis' Hospital, to which he was admitted on account of his psychotic condition, he was over-active and interfering, and refused to conform with ward discipline, becoming excited, noisy and abusive when efforts were made to restrain his activities.

On admission to Cane Hill Hospital he was in very poor health and was emaciated. He was found to have a hard palpable mass in the epigastrium beneath the left costal margin. Otherwise, except for some external hæmorrhoids, no noteworthy physical signs of disease were discovered. The blood Wassermann and M.K. reactions were negative. His physical condition steadily deteriorated and he vomited occasionally and lost weight. His feet became œdematous and from 10th January, 1942, the œdema increased rapidly until his death on January 20th.

Mental Condition: On admission he appeared elated, garrulous, rambling, and grandiose, expressing a variety of delusions, such as, that he was wealthy and talented, and could achieve great things if his family were not bent on thwarting him. He would have been a great success as an actor if he had been allowed to go on the stage, or as a bishop if he had gone in for the church; he offered to give the Medical Superintendent £1,000 if he needed the money. He was orientated as to time, space, and his own personality, although he completely lacked insight into his conduct. At this time there were no signs of confusion. The diagnosis, as stated in a certificate forwarded to the Board of Control, was: "Attack of mania."

During the period between 19th to 25th August, his emotional state remained much the same, although on two occasions for a short time it changed into one of misery during which he made no effort to answer questions, being mute and inaccessible. On September 2nd he was still elated, showing flight of ideas and grandiose delusions. He was often unsociable with the other patients and still lacked insight. Towards the end of September short periods of confusion occurred for the first time, although they did not really affect his generally manic condition. They increased somewhat in frequency and duration during October, when he appeared to be hallucinated at times and also to be deteriorating intellectually. During December confusion and memory defects progressively dominated the mental picture, although he remained elated apart from occasional depressed phases. In the last days of his life, when his

* This case has been briefly demonstrated and discussed at a meeting of the Psychiatric Section of the Royal Society of Medicine on 15th February, 1944.

physical condition progressively failed, he became somnolent and died on 20th January in a state of coma. Nothing was noted in his case history about disturbances of water and carbohydrate metabolism or of temperature regulation.

The autopsy confirmed the diagnosis of carcinoma of the stomach. The brain was sent to the Central nucleus. Fig. 1 and 2 showconsiderable gliosis Pathological Laboratory for histological investigation.

Macroscopic inspection of brain.—Weight 1,500 gr. after relatively short fixation in formalin. Convolutional pattern well preserved. Considerable thickening of leptomeninges at the base of the brain, particularly within the interpeduncular space. The basilar arteries showed some thickening of walls and rigidity, but no atheroma. On coronal dissection of the cerebrum nothing abnormal was seen except small criblures in parts of the white matter. The hypothalamus was not cut, but embedded as a whole in celloidin. All parts of the cerebellum presented a peculiar appearance. There was no genera reduction in size, but a glassy appearance was noticed in what would correspond to the granular layer. While in normal specimens only cortex and white matter of the lobules are distinguishable, in this case, thus, three conspicuous layers were noticed.

Histological investigation

Hypothalamus.—Slight changes were seen in the nuclei of the parolfactory region including the nucleus of the diagonal band. These consisted of patchy glial and mesodermal proliferation leading to some degree of cortical disorganization and unspecific degenerative changes in the nerve cells. The main lesion began, however, at a slightly more caudal level, at the rostral end of the paraventricular and vascular proliferation around the optic recess and the anterior tip of the 3rd ventricle. Part of the ventricle in this plane is without ependymal lining, but trabeculi of mesodermal tissue are seen traversing the cavity. The unusual separation of the optic recess and the rest of the 3rd ventricle by a band of gliol tissue is due (as was kindly confirmed by Prof. le Gros Clark) to the oblique direction of the original cut. The rostral end of the paraventricular nucleus is heavily involved in the glio-mesodermal reaction, most of its nerve cells showing definite signs of severe degeneration, although their characteristic appearance is still recognizable with higher magnification. The same applies to the rostral end of the supraoptic nucleus (Fig. 2) and the medial and lateral preoptic area.

FIG. 1.—Nissl stain, ×14. Hypothalamus, supraoptic portion. Heavy glio-mesodermal proliferation around 3rd ventricle.

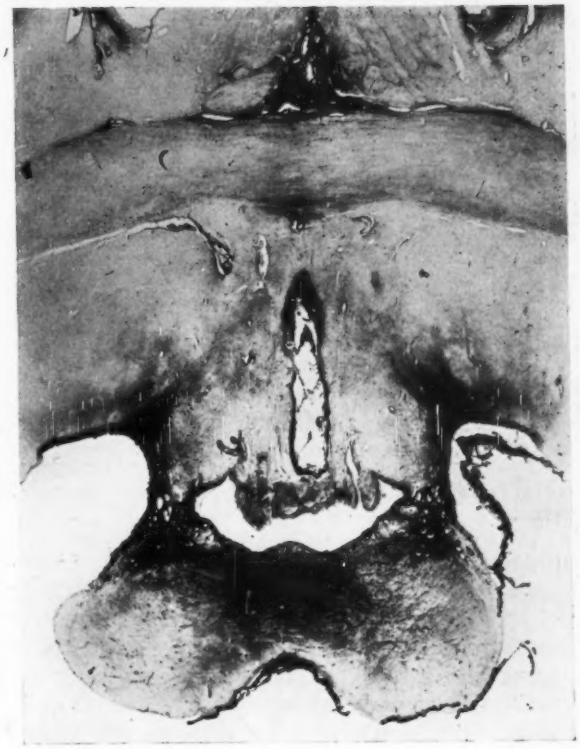

FIG. 2.—Holzer stain, ×6. Hypothalamus supraoptic portion. Severe gliosis around 3rd ventricle and optic recess. The chiasma is heavily involved.

The chiasma itself shows marked gliosis and vascular proliferation in its dorsal and dorsolateral aspect (Fig. 2). The gliosis extends around the optic recess and becomes very marked in the region of the supraoptic nucleus. No calcificaton of blood vessels is seen at this level. In addition to these more chronic lesions, areas of recent " paling " with focal outfall of cells or cell " shadow " formations are occasionally seen, but typical ischæmic or homogenizing cell degeneration have not been found.

If one proceeds in serial sections further backwards changes are seen in almost every hypothalamic centre. Nowhere, however, do they approach the extent of the anteriorly located lesions described above. The most constant and very unusual finding is calcification of small and medium-sized blood vessels (Fig. 3). This is seen in the dorsomedial ventro-medial, and supraoptic nuclei, in and near the paraventricular nuclei, tuberal nuclei, chiasma and optic tracts, median eminence, fornices and, occasionally, in other subependymal parts of the 3rd and lateral ventricles. The cellular configuration at the level of the posterior part of the

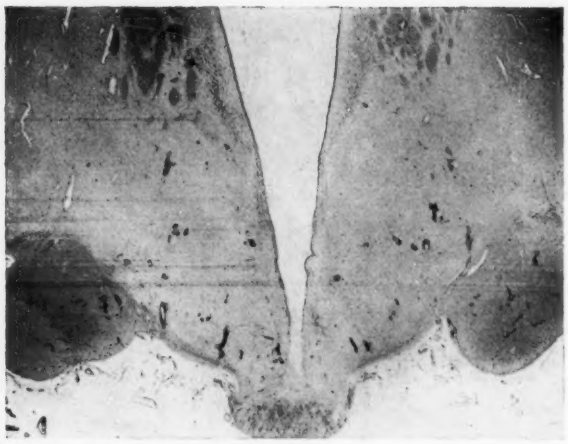

FIG. 3.—Kossa stain for calcium, ×5. Hypothalamus, tuberal portion. Calcification of numerous small blood vessels.

supraoptic and the tuberal portion of the hypothalamus is much less affected than the anterior portion. Note, for instance, the approximately normal appearance of the tuberal region (Fig. 4). Many of the nerve cells, however, show moderate degenerative changes, but rarely severe and ischemic changes. Fig. 4 shows some focal reduction within the supraoptic nucleus at the tuberal level, together with some excess of glial and vascular proliferation noticeable under high magnification.

The caudal or mamillary portion of the hypothalamus is least affected. The lateral hypothalamic nucleus and its condensation of large cells called by some writers mamillo-infundibular nucleus is almost free from change. The mamillary body gives in Nissl stained sections a pale appearance both in the medial and lateral (nucleus intercalatus of several authors) nuclei (Fig. 5). High-power examination reveals degeneration of nerve cells, a proportion of which show various stages of ischæmic change. There is very fine and recent glial fibrosis throughout the centre, but only an abortive proliferation of vessel wall elements. No calcification of vessels is seen, nor, in myelin preparations, any degeneration of the mamillo-thalamic tract.

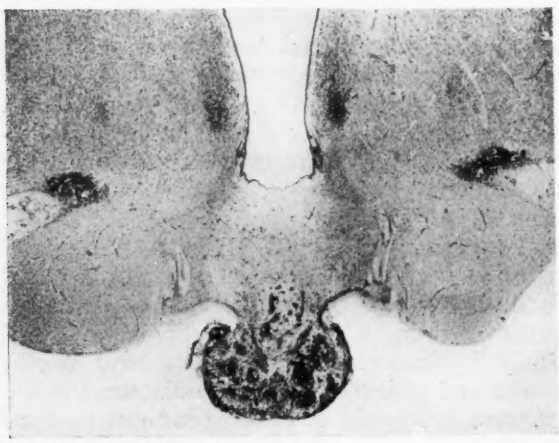

FIG. 4.—Nissl stain, × 6. Hypothalamus, tuberal portion.

The pia-arachnoid membrane in the interpeduncular space was considerably thickened, as was already noticed on macroscopic inspection. This showed most conspicuously in Van Gieson preparations where the recent increase of collagen containing fibrous tissue stained a bright red colour. The vessel walls were fibrosed; only occasionally were early atheromatous changes seen. The fibrous tissue in and around the infundibular stalk and also between the latter and the chiasma showed recent proliferation.

Brain Stem.—There were changes in the quadrigeminal region and in the inferior olives. Early gliomesodermal proliferation was seen in the grey matter around the aqueduct and within the posterior colliculi. Nerve cell changes of the acute, severe, and occasionally ischæmic type were seen. Occasionally diseased nerve cells recalled the appearance of gemistocytic glial cells. Stern (1933) has pointed out that this change is peculiar to this region and may denote an interference with the blood supply. In parenthesis, it may be mentioned that apparently similar nerve cell changes have been seen in the mamillary body by Neubuerger (1931) and Bodechtel and Gagel (1931).

FIG. 5.—Nissl stain, ×26. Mammillary body.

The changes in the inferior olives will be described and discussed in a later section of this paper.

Cerebellum.—In Nissl preparations the Purkinje cell layer stands out distinctly owing to a failure of the granule cell layer to stain with basic dyes (Fig. 6). With high-power magnification it was seen that many of the granule cells had disappeared while others stained faintly as shadows or clumps

of granular debris indicating advanced degeneration. In other places the remaining granule cells seemed to be swollen and displayed the tendency of clustering together which has been aptly called conglutination. The Purkinje cells were also diminished in number, a few exhibited various forms of degeneration, but both ischæmic and homogenizing changes were absent. The Bergmann glial cells were considerably increased in number and showed signs of recent activity, but nowhere was the

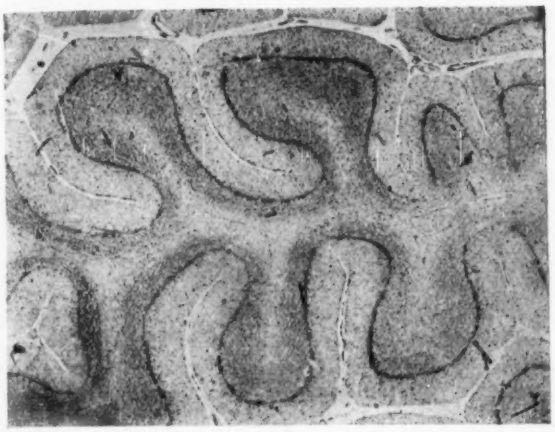

FIG. 6.—Nissl stain, ×12. Cerebellum. Note disappearance of the granular cells.

characteristic shrub-like appearance of proliferated microglia seen in the molecular layer.

Myelin preparations revealed poverty of fibres in the granule layer, and also some slight diffuse or patchy reduction in the white matter of the lobules. More fibres were seen within the granular layer after Bielschowsky impregnation which showed the normal formation of baskets, a few of which appeared to be empty. The Bergmann glia cells contained excess of lipoids. Much fat was also seen in glia cells and in mesodermal elements of the granule cell layer and, to a lesser degree, of the white matter. Impregnation for microglia did not demonstrate any appreciable proliferation nor was there much fibrous gliosis in Holzer preparations except in the white matter which contained some areas of patchy astrocytic proliferation. The dentate nucleus was little affected apart from excess of lipofuscin in nerve cells and some degree of patchy glial proliferation.

Cerebral Hemispheres.—The most striking change was a moderate fibrosis of blood vessels in the meninges as well as in the brain. In the white matter a definite rarefaction of the issue in close vicinity to the thickened vessels has produced the picture of small "criblures." An accumulation of corpora amylacea was often seen. No appreciable outfall of cortical nerve cells was noted, nor was there any certain increase of glial cells. The lipoids in neurones, glial cells and vessel wall elements corresponded in amount to the age of the patient. Neither neurofibril change nor senile plaques were observed after Bielschowsky staining. No noteworthy change, apart from subependymal calcification of blood vessels already reported, was seen in the striate body, globus pallidus, thalamus, and the remaining centres of the basal ganglia.

DISCUSSION

Diagnosis

There is little doubt that the case, despite some unusual features, is one of Wernicke's syndrome. The development, in the course of a severe gastric disease, of mental symptoms, characterized by confusion, hallucinations, and memory defect, and terminating in coma and death, combined with the pathological finding of a lesion in the hypothalamic area, puts the diagnosis of Wernicke syndrome on a solid basis. Clinically the psychosis was atypical, and the significance of its unusual features in relation to the pathology will be discussed in a later section. The unusual pathological features include the prevalence of advanced lesions in the anterior part of the hypothalamus and degeneration resulting in calcification rather than proliferation of blood vessels. The present writer has been unable to trace any previous report in the literature of calcification of hypothalamic blood vessels in cases of Wernicke's disease. It is interesting to note that Campbell and Biggart (1939) included the optic nerves among the vulnerable structures in the Wernicke syndrome. The lesion in their case 11, was, however, in the nature of softening, whereas in the case described in this paper, gliosis and abundant calcification of blood vessels in the optic tracts was noted. Much calcification was found in the subependymal regions of the 3rd and lateral ventricles and the median eminence. There was no calcification in the caudal (mamillary) part of the hypothalamus; the mamillary body was seen undergoing ischæmic nerve cell degeneration without vascular proliferation. Such absence of the vascular proliferation has been occasionally noted before (Neubuerger, 1931).

In only one of my five cases was there a slight late involvement of the quadrigeminal region, and in no case were the vestibular and vagal nuclei affected. These centres are known to be susceptible in Wernicke's syndrome. The lesions in the cerebellum and inferior olives and their significance will be the subject of separate paragraphs.

It is worth mentioning that the nerve cell change known as primary irritation, which is so prominent in pellagra, has not been seen in any of my cases, nor have manifestations of Wernicke's syndrome been encountered in my pellagra material. This interesting and surprising mutual exclusiveness will be the subject of a separate paper.

The manic syndrome in lesions of the hypothalamus

The psychotic manifestations associated with the Wernicke syndrome are usually of the confusional type which when becoming chronic passes over into a typical Korsakow's psychosis. Many authors believe that the affection of the mamillary body is invariably associated with Korsakow's psychosis (Kant, 1932/33). In our material, confusional states, Korsakow syndrome, somnolence and coma

dominate the psychiatric picture with the exception of the one case which has been described in full and in which also the localization of the lesion within the hypothalamic area appeared to be significantly different. In the case, described in detail in this paper, the psychosis presented for three months (July–September, 1941) all the characteristics of a manic syndrome with only two short intervals of depression. From the end of September onwards confusion, hallucinations, memory defect and intellectual deterioration gradually supervened, slightly at first, and slowly increasing until in January, 1942, the patient became somnolent and died in coma.

The incidence of manic syndromes and rage-like excitement in hypothalamic lesions has been recently discussed (cf. reviews by Grinker, 1939; Ranson and Magoun, 1939; Alpers, 1940; Kennedy, 1940). In brief, the experimental and pathological evidence so far available is as follows:

Bard (1928) produced sham rage in cats whose cortex and cranial half of the hypothalamus had been ablated. These outbursts of rage resembled the behaviour of the infuriated normal animal and were not comparable with the pseudoaffective reflexes obtained in cats after section of the midbrain. According to the author the mechanism responsible for sham rage lies within an area comprising the caudal half of the hypothalamus and, possibly, the most ventral and caudal fraction of the corresponding segment of the thalamus. Fulton and Ingraham (1929) placed lesions in cats anteriorly to the chiasma. They believed that the rage reaction produced in three out of four cats was due to division of fronto-hypothalamic tracts. In this regard some more detailed information has been given by Spiegel, Miller, and Oppenheimer (1940). They experimented on cats and dogs with a view to studying those parts of the forebrain which send impulses to the hypothalamus. Lesions of the frontal pole merely produced hypermotility, whereas definite manifestations of rage appeared if the lesions involved the olfactory tubercles. Destruction of the olfactory bulbs and their stalks had only slight and transitory effect. These authors were also able to produce rage after bilateral lesion of the amygdaloid nuclei and the hippocampus-fornix system. In the discussion which followed the paper Papez (1940) reported the production of drowsiness and twilight states in cats by removal of the anterior portion of the cingular gyrus. The work of Klüver and Bucy (1939) was also mentioned; they failed to produce rage in monkeys after bilateral ablation of the temporal lobes. They observed, however, an absence of emotional reaction if the temporal tissue which had been removed contained the hippocampal region. Ranson and his collaborators were primarily interested in the production of somnolence and catalepsy (Ranson and Ingram, 1932; Ranson, 1939; Ranson and Magoun, 1939). Bilateral lesions in the lateral hypothalamic areas extending to the caudal border of the mamillary bodies were most effective in producing somnolence, while catalepsy followed if the lesion damaged the ventral part of the brain stem from the posterior part of the hypothalamus to the 3rd nerve. If, however, the lesions were placed more anteriorly in the lateral hypothalamus, as was done in six monkeys, the animals were only temporarily drowsy and then became increasingly wild. In none of these six animals were the mamillothalamic tracts, mamillary nuclei, posterior hypothalamic nuclei, or the posterior part of the lateral hypothalamic area involved. Ranson and Magoun (1939) conclude, in agreement with Bard (1928), that a mechanism is located in the posterior part of the lateral hypothalamus which when activated excites the entire organism. Maniacal excitement has also been seen after very small lesions in the grey matter around the aqueduct in the plane of the midbrain. (Foerster and Gagel, 1933/34; Bailey and Davies, 1942.)

In man Foerster and Gagel (1933/34) were able to make important observations of an experimental nature during operations at the base of the brain. Temporary manic excitement occurred if the slight pressure of a swab was applied to the chiasmatic part of the hypothalamus. This was observed in four cases, and it was expressly stated that from no other position could a similar condition be elicited. Whether the manipulation was in the nature of a stimulus (as the authors believed) or that of a slight depression of normal function of this region, is, however, uncertain, but the experimental results described above would favour depression of function.

Manic syndromes supposed to be due to lesions within or near the hypothalamic area have been described in human pathological material by a number of workers (Schuster, 1902; Fulton and Bailey, 1929; Cushing, 1929; Urechia, 1934; Cox, 1937; Dott, 1938; Alpers, 1940; Vonderahe, 1940; Stern and Dancey, 1942). In most of these recorded cases the lesion was a tumour or a cyst, and precise localization was thus difficult if not impossible. Guttmann and Hermann (1932), who are widely quoted in this connection, were dealing with confusional states ("amentielle psychosen"). But their work is important in a negative sense, for they found that a lesion between the hypophyseal stalk and the anterior border of the pons—that is to say, in the caudal part of the hypothalamus—is responsible for this type of confusional psychosis. Cases and syndromes described by Schilder and Weissmann (1927), van Bogaert (1927), and L'hermitte, Levy and Trelles (1932), obviously belong to the same category. This apparently applies also to the case of akinetic mutism published by Oldfield, Cairns, Pennybacker and Whitteridge (1941), in which there was a cyst of the 3rd ventricle and to two cases showing traumatic stupor described by Jefferson (1944), in both of which the cerebral hemispheres and the anterior half of the hypothalamus were, significantly, found to be normal. The contributions to the problem made by Kleist (1934) cannot be dealt with in detail, as his book was not accessible to the present writer. In a subsequent paper, however, Kleist (1937) states that

excitement may be produced by frontal lesions involving the anterior part of the diencephalon and hypothalamus, whereas general depression of function and stupor is caused by temporal, parietal, or occipital lesions involving (directly or by pressure) the posterior part of the diencephalon. The criticism has been made against Kleist that his views are based mainly on macroscopic investigations.

My own case is not only in agreement with the results of previous experimental investigation, but shows the essential clinico-pathological relationship with greater clarity than any of the human cases previously reported in association with the manic syndrome. In this case of atypical Wernicke's syndrome in which a manic syndrome prevailed for three to four months of a total psychotic period of six months, it is seen that, contrary to the usual pathological findings, the more severe lesions were placed in the anterior (supraoptic) portion of the hypothalamus. Fig. 7 indicates the striking

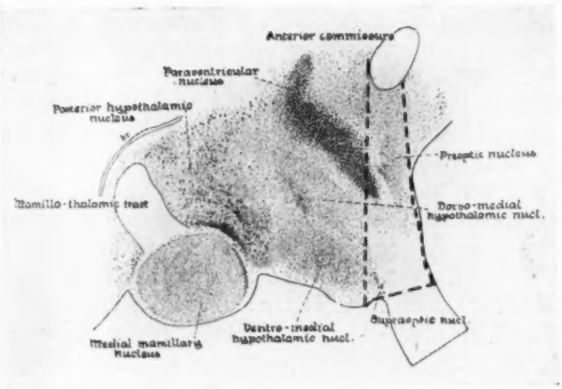

FIG. 7.—Diagram reproduced after modification from Le Gros Clark (*The Hypothalamus*, Oliver and Boyd, Edinburgh). The dotted lines indicate approximately the extent of the severe lesion.

similarity of the localization of the lesion in our case with those produced experimentally by Fulton and Ingraham (1929) and Ranson and his school (cf. Ranson and Magoun, 1939). The possible objection that the Wernicke syndrome is a rather acute condition lasting as a rule for not longer than a few weeks can be met by the fact that the histological lesions are unusually chronic in appearance as exemplified by the heavy fibrous gliosis and extensive calcification of small blood vessels. Moreover, there may have been preceding the histologically visible lesion a local metabolic effect arising from the thiamine deficiency and setting up what is now often referred to as a biochemical lesion.

In recording this case as a human counterpart to experimentally produced rage it is impossible to over emphasize the extraordinarily complex and controversial nature of the problem. In the discussion following Kleist's (1937) paper, it was said that attempts to localize psychological function (apart from the gross loss seen in dementia) will always remain in the "anteroom of the mind." Whether or not this general statement is true it is, in substance at least, in line with much recent criticism directed against attempts to regard the hypothalamus as a centre of emotion, personality make-up, consciousness and other vital mental processes (Kleitman, 1939; Grinker, 1939; Alpers, 1940; Masserman, 1942, 1943; Jefferson, 1944). On the strength of personal and other experimental work Masserman emphatically rejects all theories which postulate a localization of emotional experience in the hypothalamus, whose only established rôle is to reinforce and co-ordinate the neural and hormonal mechanisms of emotional expression. According to this author emotion is a "highly integrated conative, cognitive, and affective somatic reaction in which not only the central nervous system but the entire organism functions as a psychobiologic whole."

It is therefore imperative to consider hypothalamic function and dysfunction in its wider anatomical and physiological implications. Several connections with the frontal cortex have been either established or are likely to exist (1) Prefrontal cortex—dorsomedial thalamic nucleus—periventricular fibre system passing to the posterior hypothalamic area; (2) frontal cortex—septal nuclei—septohypothalamic tract; (3) frontal cortex—zona incerta—mamillary region; (4) parolfactory cortex—medial forebrain bundle—hypothalamus. The mamillary body is connected with the anterior part of the cingular cortex via the mamillo-thalamic tract and anterior thalamic nucleus, and with the pyramidal cells of the Ammon's horn via the fornix system. Lastly the hypothalamus maintains important connections with caudal centres in the brainstem and with the pituitary gland. Many of the centres linked with the hypothalamus are part of the rhinencephalon, but it is unlikely that all are concerned with olfactory function. The Ammon's horn and anterior cingular gyrus (anterior limbic region) are more highly differentiated in man than in any of the lower mammals (Rose, 1935). The gyrus cinguli has been considered to be the cortical representation of the vegetative nervous system by Economo and Koskinas as long ago as 1925 (quoted from Rose, 1935).

It is interesting, in the light of these observations, that Papez (1937, 1940) regards the hypothalamus, parolfactory region, amygdaloid nuclei, anterior thalamic nuclei, cingular cortex, and the hippocampus as members of a "well interconnected and harmonious mechanism which may elaborate the functions of central emotion as well as participate in emotional expression." Obviously, this concept refers to conditions in animal brains; in fact, in its present form, it was outlined by the author in the discussion which followed a report on their experimental work by Spiegel, Miller and Oppenheimer (1940, loc. cit.). In Kleist's (1934, 1937) scheme which is based on human experiences, various regions in the frontal lobe combine with the cingular gyrus and hypothalamic and thalamic levels to form the structural basis of personality organization. His views have been hotly disputed, particularly on the grounds of his rigid dogmatism, but it cannot be denied that most of the theories

which have been recently developed to explain the mechanism of prefrontal leucotomy are based on similar conceptions.

Electrophysiological evidence seems to support the interrelationship of the hypothalamus with other regions of the brain. Measuring thermal relations by means of thermo-electric couples, Serota (1939) found increase of heat in the hypothalamic area after induction of emotion such as fear, rage, or anticipation of food. It has been shown that electrical stimulation of the hypothalamus (in animals and man) may result in massive cortical discharges (Grinker and Serota, 1938; Ranson and Magoun, 1939), whereas destruction abolishes all cortical activity (Grinker and Serota, 1938; Obrador, 1943). Although these results require confirmation, it can be confidently expected that electroencephalography will play a major part in the further elucidation of these problems.

This close inter-relationship may, perhaps, explain why a lesion in or near the hypothalamic area might break up complex patterns of emotional behaviour, although the hypothalamus itself is solely concerned with emotional expression. A lesion placed at or in front of the rostral portion of the hypothalamus would be particularly likely to disrupt frontohypothalamic connections. Phylogenetic differentiation tending to increase frontal preponderance may possibly account for some of the differences between manic syndromes in man and the primitive rage reactions of experimental animals.

In view of the difficulty of a satisfactory explanation some workers (Riddoch, 1938; Stern and Dancey, 1942) have postulated a constitutional factor in addition to the affection of the hypothalamus. This is in keeping with the popular assumption that an intrinsic factor is in operation whenever symptoms of an endogenous psychosis—mania, depression, schizophrenia—occur in the course of an organic disease of the brain. In the case investigated by Stern and Dancey (1942) positive hereditary evidence was available. The only constitutional taint in our case is that the sister of the patient is a mental defective inclined to occasional depressions of an apparently reactive type. The acceptance of a hereditary determination need not necessarily invalidate the pathogenic significance of the hypothalamic lesion. It is conceivable that subtle and reversible abnormalities underlie "functional" mania and that they are localized in the same cerebral system which is the site of histological lesions in certain organic cases displaying manic symptoms. The time may come when it will be possible to express some constitutional factors in terms of regional susceptibilities of vital centres and mechanisms in the brain and other systems.

A final answer to all these difficult questions will not be given by speculation, however intriguing this may be, but by further experimental and pathological work. In view of the obvious phylogenetic differences, the investigation of human brains containing circumscribed lesions of the relevant centres will be especially valuable. These latter studies should be undertaken irrespective of the mental symptomatology in order to avoid selection of positive cases only. It is with a view to contributing to this collection that my case is presented for publication.

The cerebellum in vitamin deficiency

The cerebellar lesion in our case requires a few remarks. In only one of the five cases on which this paper is based was the cerebellum affected, and the present writer does not recall a description of cerebellar change with a similar selective action on the granules in the literature upon nutritional deficiencies. In chronic alcoholism, with or without the Wernicke syndrome, most writers either failed to find cerebellar lesions (Stevenson, McGowan and Allen, 1941), or described only circumscribed lobular atrophy with degeneration of the Purkinje cells (Neubuerger, 1931). In experimental thiamine deficiency, petechial hæmorrhages may occur in the cerebellum together with the changes in other regions characteristic of the Wernicke syndrome (cf. Wolbach and Bessey, 1942). Gross hæmorrhages in various parts of the brain including the cerebellum have been produced by Jervis (1942) in choline-deficient rats. Alexander (1941), who made an attempt at correlating the various neuropathological lesions with the pathogenic factors operative in chronic alcoholism, is inclined to ascribe an affection of the cerebellum to deficiency of α-tocopherol. It is true that in newly hatched chicks this deficiency may lead to an ischæmic necrosis characterized by œdema, rapid necrosis of the neurones and of the glia, but it is neither found in adult animals nor in man (Pappenheimer, 1942; Wolf and Pappenheimer, 1942). In none of our cases of histologically verified pellagra was a cerebellar lesion of the type under discussion seen. Only in one doubtful case did the cerebellum display major changes, but their relationship to the pellagra-preventing factor remains to be proved.

A more or less selective degeneration of the granular layer has been described after prolonged experimental CO poisoning (Ferraro and Morrison, 1928), in various toxic-infectious conditions including experimental lead, carbon monoxide, and histamine poisoning, experimental inanition, septic meningitis, etc. (Williams, 1934), and quite recently by Winkelman (1943) in one case of diabetes dying from hæmorrhagic gastritis and intestinal gangrene, and in another diagnosed as mania. The histological appearance is that of fusing of the granular cells into smaller and larger clumps (conglutination) and subsequent degeneration and disappearance in cases of longer standing.

An interesting light on the pathogenesis of this type of lesion is thrown by recent poisoning experiments with thiophen (Upners, 1939). It has been shown earlier that after massive doses of this substance the Purkinje cells undergo ischæmic or homogenizing degeneration. Using small doses over long periods, Upners found a selective action

on the granular layer resulting in degeneration. At the same time he noticed changes in the quadrigeminal region which, in his opinion, closely resembled those seen in the Wernicke syndrome. Unfortunately, his clinical notes were only brief, but he mentioned that the prolonged poisoning resulted in frequent vomiting and complete anorexia in his animals.

There is, thus, some suggestion that a nutritional factor might be operative in the production of selective granular degeneration. A final decision must be deferred, however, until more convincing evidence is available. The problem in its broader aspects is, at present, under investigation in this laboratory.

Changes in the inferior olives

In four out of our five fully examined cases of the Wernicke's syndrome changes were found in the inferior olives. They are illustrated in Figs. 8–12. Fig. 8 shows an approximately normal olive as control. Fig. 9 is taken from the case of gastric carcinoma. It is easily seen with low magnification that there is a diminution of nerve cells which is most conspicuous in the dorso-medial corner of the centre. High-power inspection reveals that all nerve cells show some pigment degeneration, but in the dorso-medial corner they become opaque discs with the nuclei either dark and shrunken or breaking up into granules. This is the cell change known as homogenizing degeneration. There is considerable gliomesodermal reaction (" gliarasen," activated astrocytes, endothelial proliferation) in this corner, and in Holzer preparations a moderate diffuse glial fibrosis is seen. No demyelination was noted. Fig. 10 shows an almost complete loss of nerve cells with low magnification. With higher magnification many nerve cells are still recognizable in advanced condition of homogenizing degeneration. There is also heavy glial and endothelial reaction and severe gliosis in Holzer preparations. The photograph is taken from a case of Wernicke's syndrome in pernicious anæmia. Fig. 11 illustrates a picture, seen in the caudal part of the inferior olives in a case of Wernicke syndrome after hyperemesis gravidarum. Here again the dorso-medial corner is especially affected. The transition from less affected to the severely damaged part within the dorsal band is shown with higher magnification in Fig. 12. Towards the rostral end of the centre, the whole olive is involved. Histological detail is much the same as in the previous cases, that is to say, the principal features are homogenizing degeneration of nerve cells, and glio-mesodermal reaction. The homogenizing cell disease is particularly characteristic. Many naked triangular nuclei with swollen nucleolus are seen as remainders of the affected cells. Again, there is no demyelination. In a last case (pernicious anæmia) the only local sign of olivary involvement is a glial nodule in the mediodorsal corner, but there is some general gliamesodermal activity throughout the centre.

Lesions of the inferior olives of the type described have been first studied systematically by von Braunmühl (1928, 1929, 1930) in a variety of conditions. Von Braunmühl regarded them as a manifestation of a system disease of the centre, but later, impressed by the type of cell degeneration and glio-mesodermal repair, he inclined more to a vascular pathogenesis, and as such they have been accepted by many workers especially of the German school. Subsequently, Neubuerger (1931) described identical changes in the olives of alcoholics (his cases 1, 2, 7, 17, 23, 28), in most of which the typical mamillary changes were also seen. Kant (1932/33), Campbell and Biggart (1939) and Alexander (1940) do not mention the olives as vulnerable centres in the Wernicke syndrome. In our own material four out of five fully investigated cases displaying mammillary changes of varying degree had changes in the olives, and it is interesting that none of the cases had an alcoholic history, but had acquired the lesion in the course of pernicious anæmia, hyperemesis gravidarum and severe gastric disease. Scrutinizing von Braunmühl's clinical records one is struck by the frequency with which he found the olivary changes in conditions which are known to facilitate nutritional deficiency (protracted pyæmia, sepsis following abortion, typhoid and paratyphoid fever, postencephalitis after long fever therapy). In only one case (glioma of temporal lobe with intense œdema) was there no evidence of a possible nutritional factor. In a fairly large sample of anoxic and vascular conditions, the present writer failed to find olivary changes of this type, nor was this type of olivary degeneration seen in a large series of cases dying in the course of postencephalitis. The only condition in which a comparable change was found was a case of subacute yellow atrophy of the liver.

All this is strongly suggestive of a nutritional factor in the pathogenesis of the olivary lesions. It must be left undecided whether thiamine or some other factor, alone or in combination, is responsible. The histological appearance of the olivary changes is certainly different from that in any other region vulnerable in thiamine deficiency, the main point of difference being the absence of the characteristic primary proliferation of blood vessels. The vascular proliferation must be regarded as secondary to the parenchymatous degeneration. Furthermore, there is no parallelism in the intensity of the lesions. Our alcoholic case with heaviest mammillary damage showed no involvement of the inferior olives, and none of the other vitamins is known to cause olivary lesions if deficient, while in all cases of human pellagra available for investigation at this laboratory the olives were found intact. The identification of the factor responsible for the olivary lesion must be left to specially designed animal experiments.

It is difficult to account for the special susceptibility of the dorso-medial part of the centre. Von Braunmühl has been at a loss to explain it by peculiarities of the blood supply. Olive changes may be secondary to cerebellar degeneration and it is assumed that the olivary axons terminate as

FIG. 8.—Nissl stain, ×14. Normal inferior olive.

FIG. 9.—Nissl stain, ×15. Inferior olive showing degeneration and outfall of nerve cells especially in the dorso-medial corner.

FIG. 10.—Nissl stain, ×21. Inferior olive. Generalized outfall of nerve cells.

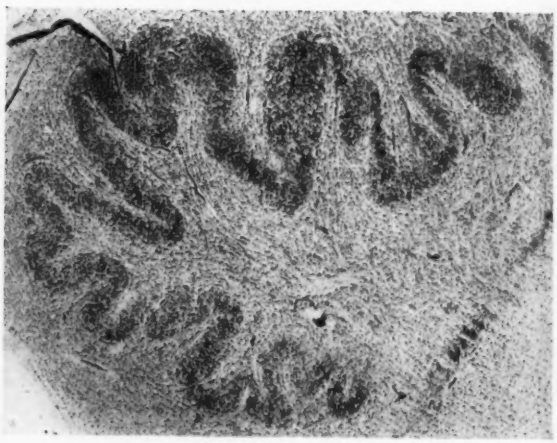

FIG. 11.—Nissl stain, ×20. Inferior olive. Degeneration in dorso-medial corner.

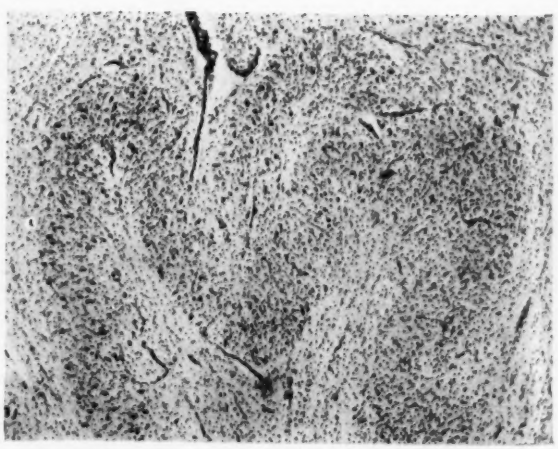

FIG. 12.—Nissl stain, ×36. The same as Fig. 11, with higher magnification to demonstrate the contrast between severely damaged (right) and better preserved part of the inferior olive.

mossy fibres around the dendrites of the granular cells (Parkes, Weber and Greenfield, 1942). According to these authors quoting earlier work, the dorsal part of the olives is related to the cortex of the superior surface of the cerebellum. Likewise, the medial portion of the olives has a close relation to the palæocerebellar cortex. However, in three of our cases with olivary lesions the cerebellum was histologically normal while in the fourth the cerebellar lesion was ubiquitous. This suggests that the affection of the inferior olives is independent from a histologically recognizable lesion of the cerebellum.

Summary

A pathological investigation has been made in seven cases presenting the Wernicke syndrome. In two cases there was a history of alcoholism and in three of pernicious anæmia, in one the condition followed hyperemesis gravidarum and in one it followed gastric carcinoma.

The last case has been described in full, as it was distinguished by an atypical clinical course in which mania was present for a considerable time. It is important that the oldest and severest lesions were localized in the anterior portion of the hypothalamus. The incidence of manic syndromes associated with hypothalamic lesions has been discussed in the light of previous experimental and pathological observations.

The same case of gastric carcinoma had a peculiar cerebellar lesion affecting predominantly the granular layer.

In four out of the five cases which were fully investigated inferior olives were damaged in a characteristic way, the neurones of the medio-dorsal corner undergoing homogenizing degeneration. The possibility of a deficiency factor in the pathogenesis of the olivary lesions has been discussed.

I wish to thank Drs. Lilly and Cook for their valuable help in collecting clinical data of one case, and Mrs. Beck for the preparation of slides and microphotographs.

REFERENCES

Alexander, L. (1939). *Arch. Neurol. Psychiat.*, **42,** 1172.
—— (1940). *Amer. J. Pathol.*, **16,** 61.
—— (1941). *Quart. J. Stud. on Alcohol*, **2,** 260.
——, Green, R. G., Evans, C. A., Wolf, L. E. (1941). *Tr. Amer. neurol. Ass.*, **67,** 119.
Alpers, B. J. (1940). *Proc. Ass. Res. nerv. ment. Dis.*, **20,** 725.
Bailey, P., and Davies, E. W. (1942). *Proc. Soc. exp. Biol. N.Y.*, **51,** 305.
Bard, P. (1928). *Amer. J. Physiol.*, **84,** 490.
Bodechtel, G., and Gagel, O. (1931). *Z. ges. Neurol. Psychiat.*, **132,** 755.
Campbell, A. C. P., and Biggart, J. H. (1939). *J. Path. Bact.*, **48,** 245.
Cox, L. B. (1937). *Med. J. Aust.*, **1,** 742.
Cushing, H. (1929). *The pituitary body and hypothalamus.* C. C. Thomas, Springfield.
Dott, N. M. (1938). *The Hypothalamus.* Oliver & Boyd, Edinburgh.
Evans, C. A., Carlson, W. E., and Green, R. G. (1942). *Amer. J. Pathol.*, **18,** 79.
Ferraro, A., and Morrison, R. (1928). *Psychiat. Quart.*, **2,** 506.
Ferraro, A. and Roizin, L. (1941). *Tr. Amer. neurol. Ass.*, **67,** 177.
Foerster, O., and Gagel, O. (1933/34). *Z. ges. Neurol. Psychiat.*, **149,** 312.
Fulton, J. F., and Bailey, P. (1929). *J. nerv. ment. Dis.*, **69,** 1; 145; 261.
Fulton, J. F., and Ingraham, F. D. (1929). *J. Physiol.*, **67,** 27.
Grinker, R. R. (1939). *Psychosomat. Med.*, **1,** 19.
—— and Serota, H. (1938). *J. Neurophysiol.*, **1,** 573.
Gutmann, E., and Herrmann, K. (1932). *Z. ges. Neurol. Psychiat.*, **140,** 439.
Jefferson, G. (1944). *Brit. med. J.*, **1** (with leading article, p. 15).
Jervis, G. A. (1942). *Proc. Soc. exp. Biol. Med.*, **51,** 193.
Kant, F. (1932/33). *Arch. Psychiat. Nervenkr.*, **98,** 702.
Kennedy, F. (1940). *Proc. Ass. Res. nerv. ment. Dis.*, **20,** 864.
Kleist, K. (1934). Vol. 4, *Handbuch arztl. Erfahrungen im Welt Kriege.* A. Barth, Leipzig.
—— (1937). *Z. ges. Neurol. Psychiat.*, **158,** 159.
Kleitman, N. (1939). *Sleep and wakefulness.* Chicago.
Klüver, H., and Bucy, P. C. (1939). *Arch. Neurol. Psychiat.*, **42,** 979.
L'hermitte, I., Levy, G., and Trelles, I. (1932). *Rev. Neurol.*, **1,** 382.
Masserman, J. H. (1942). *Amer. J. Psychiat.*, **98,** 633.
—— (1943). *Behavior and Neurosis.* University of Chicago Press.
Neubuerger, K. (1931). *Z. ges. Neurol. Psychiat.*, **135,** 159.
—— (1937). *Ibid*, **160,** 208.
Oldfield, R. C., Cairns, H., Pennybacker, J. R., and Whitteridge, D. (1941). *Brain*, **64,** 273.
Obrador Alcalde, S. (1943). *J. Neurophysiol.*, **6,** 81.
Pappenheimer, A. M. (1942). *Amer. J. Pathol.*, **18,** 169.
Papez, J. W. (1937). *Arch. Neurol. Psychiat.*, **38,** 725.
—— (1940). *Tr. Amer. Neurol. Ass.*, page 128.
Prickett, C. O. (1934). *Amer. J. Physiol.*, **107,** 459.
Ranson, S. W. (1939). *Arch. Neurol. Psychiat.*, **41,** 1.
—— and Ingram, W. R. (1932). *Amer. J. Physiol.*, **101,** 690.
—— and Magoun, H. W. (1939). *Ergebn. Physiol.*, **41,** 56.
Riddoch, G. (1938). *The Hypothalamus.* Oliver and Boyd, Edinburgh.
Rose, M. (1935). *Handbuch der Neurologie* (Bumke–Foerster), **1,** 588.
Schilder, P., and Weissmann, M. (1927). *Z. ges. Neurol. Psychiat.*, **110,** 767.
Schuster, P. (1902). *Psychische Störungen bei Hirntumoren*, Enke, Stuttgart.
Serota, H. (1939). *J. Neurophysiol.*, **2,** 42.
Sheehan, H. L. (1939). *Proc. roy. Soc. Med.*, **32,** 581.
Sinclair, H. M. (1939). *Ibid.*, **32,** 581.
Spiegel, E. A., Miller, H. R., and Oppenheimer, M. J. (1940). *Tr. Amer. Neurol. Ass.*, page 127.
Stern, K. (1936). *Z. ges. Neurol. Psychiat.*, **154,** 521.
—— and Dancey, T. E. (1942). *Amer. J. Psychiat.*, **98,** 716.
Stevenson, L. D., McGowan, L. E., Allan, A. M. (1941). *Arch. Neurol. Psychiat.*, **45,** 56.
Upners, T. (1939). *Z. ges. Neurol. Psychiat.*, **166,** 623.
Urechia, C. I. (1934). *Rev. Neurol.*, **41,** 585.
Van Bogaert, L. (1927). *Ibid.*, **34,** 608.
Von Braunmuhl, A. (1928). *Z. ges. Neurol. Psychiat.*, **112,** 213.
—— (1929). *Ibid.*, **120,** 716.
—— (1930). *Ibid.*, **126,** 621.
Vonderahe, A. R. (1940). *Tr. Amer. Neurol. Ass.*, page 129.
Weber Parkes, F., and Greenfield, J. G. (1942). *Brain*, **65,** 220.
Williams, E. Y. (1934). *Arch. Path.*, **17,** 206.
Winkelman, N. W. (1943). *J. Neuropath. exp. Neurol.*, **2,** 413.
Wolbach, S. B., and Bessey, O. A. (1942). *Physiol. Rev.*, **22,** 233.
Wolf, A., and Pappenheimer, A. (1942). *Arch. Neurol. Psychiat.*, **48,** 538.
Zimmerman, H. M. (1939/40). *Yale J. biol. Med.*, **12,** 23.
—— (1940). *Amer. J. Pathol.*, **16,** 668.

THE EFFECT OF PERCUSSION OF NERVE

BY

D. DENNY-BROWN and CHARLES BRENNER *

(RECEIVED 8TH AUGUST, 1944)

THAT a physical impact or blow on a peripheral nerve may cause a brief and transient disorder of neural function has long been recognized. The mildest forms of such disturbance, such as occur when the ulnar nerve at the elbow is knocked, are within the experience of all. Tillaux (1866) and other early writers distinguished further degrees of *commotion* and *contusion*, but did not always distinguish transient lesions following brief impact from those associated with more prolonged physical force such as the damage to the brachial plexus resulting from dislocation of the shoulder, which were also spoken of as "commotion." Weir Mitchell (1872) speaks of contusion as resulting from a blow from a blunt instrument, and, noting that the immediate effects are transient, emphasizes the liability to delayed neuralgia, and in some cases to paralysis with delayed onset. He also noted that, as a result of mild contusions, the disturbance of function was partial, and involved sensory function more than motor.

Tubby (1915) describes "concussion" as varying from effusion of blood into a nerve to temporary anæmia or hyperæmia resulting from compression of a nerve against bone by the rapid passage of a projectile, and cites case histories illustrating the transient paralysis lasting 5, 7 and 11 weeks before complete recovery (the last an injury of the sciatic nerve at the notch) without reaction of degeneration, and with both motor and sensory changes. He also described two examples of lesions of mixed severity where some muscles, delayed in recovery, had lost faradic excitability.

In the World War 1914–18 a proportion of the nerves damaged by gunshot wound presented a fusiform enlargement, a "nerve spindle" or "pseudo-neuroma" (Tinel, 1917). Platt (1921) found such a lesion in 7 per cent. of 500 operations. The condition is also referred to in the British Medical Research Council Report (1920). Whereas asymmetrical lesion of the nerve, or extensive fibrosis covering a wide extent, may be attributed to direct laceration of the nerve by the injury or to involvement in subsequent sepsis, the nerve spindle was supposed to result from a primary contusion of the nerve by the transient passage of the projectile. It was no doubt often difficult to decide upon the actual mechanism of injury, and Dejerine *et al.* (1915) remark that the symptoms of "compression" most often had appeared at the actual moment of injury. Platt (1921) concludes that war lesion of nerves is almost always a "primary lesion" and the secondary influence of compression by perineural scarring or callus "is usually subordinate and often entirely negligible."

Tinel (1917) summarizes the findings of Dejerine and his collaborators (1915) and describes two types of nerve lesions in continuity, a *neuroma* or cicatrix with axonal proliferation proximal to a dense intraneural scar, and a *pseudo-neuroma* occurring "in certain contusions or compressions" of nerve when the laminated peripheral sheaths were not destroyed. In the latter condition he described swelling or fragmentation of the myelin, with frequent demyelination of the fibres. The axis cylinders were irregular, beaded, barbed, or in the form of a bundle of fine fibrils. There was always an interstitial infiltration of the nerve with "connective tissue" and proliferation of the sheath of Schwann. In the region of the swelling the myelin may have disappeared without interruption of axis cylinders, and without Wallerian degeneration, in other cases fibres had degenerated. He noted the association of incomplete, temporary, dissociated and irregular paralyses with such lesions. He also stated that in other cases regeneration was slow and difficult. The "syndrome of nerve irritation accompanied by trophic pains and disturbances" (causalgia) was common in association with such lesions as was also the experience of Platt (1921). In two cases of median causalgia under the care of one of us (D. D-B.) the original disorder in motor function of the median nerve following gunshot injury had been so transient as to lead to the inevitable conclusion that the primary nerve injury was a contusion. Contusion of nerve therefore has a possible but unknown part in the pathogenesis of causalgia and offers a simple starting point in this problem.

Tillaux (1866) subjected the nerves of rabbits to slight blows with a hammer and then examined the contused portion. Four days after the blow he saw hæmorrhages within the epineurium and under the perineurium, and lessening of the calibre of nerve fibres, with commencing distal degeneration.

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Weir Mitchell (1872) cites experiments on rabbits and observed that in lesser degrees of injury many fibres escaped damage. After a "smart blow" there was immediate complete paralysis and the nerve fibres at the level struck had an irregularly swollen appearance. Complete functional and structural recovery could occur in a few days. In two rabbits allowed to survive a longer period a "neuroma" developed at the site of injury. Cajal (1928) made a detailed study of the regenerative changes following a closely similar injury caused by a brief pinch of a nerve by forceps, and described necrosis of the damaged portion of the axon and rich branching of nerve sprouts within the undamaged sheath of Schwann.

In view of some doubt concerning the nature of the structural change underlying the very brief disturbance of function in lesser degrees of such lesion as described by Mitchell and others, and the relationship of such damage to that described by us in lesions of nerve caused by ischæmia and compression (Denny-Brown and Brenner 1944*a* and *b*) we have repeated the experiments of Tillaux and Mitchell in cats and made observations at varying intervals after injury.

Method

The sciatic nerve of the cat was exposed in mid-thigh under nembutal anæsthesia. The nerve was gently raised on a flat metal surface (at P in the diagram Fig. 1) and the blunt edge of a retractor

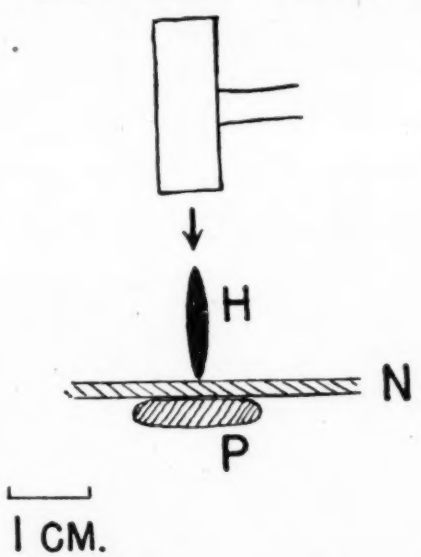


FIG. 1.—Diagram to show cross-section shape of the striker H, drawn to scale, in relation to the nerve N and underlying plate P.

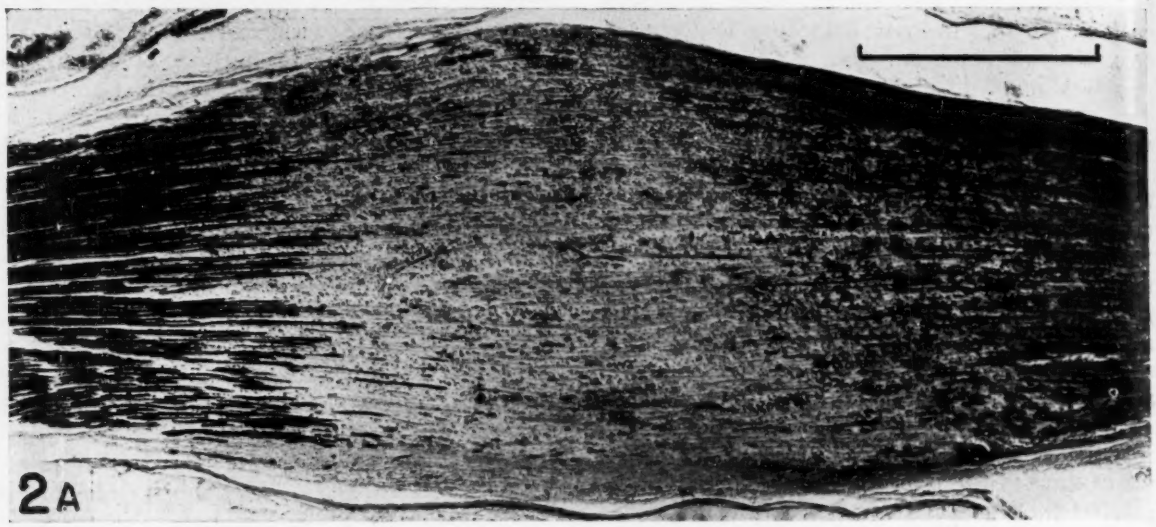
handle (cross-section to scale shown in Fig. 1 at H) was laid transversely across the nerve, and struck a sharp blow with a light hammer. On removing the instruments a narrow groove is immediately seen. The depth of the groove depends on the intensity of the blow. Our intention was to give just sufficient injury to leave a visible transverse mark on the nerve. In the next 30 seconds the nerve bordering the groove became distinctly pale and opaque, even if no hæmorrhage occurred. Within 8 to 15 seconds one or two very small streaks of hæmorrhage were often seen alongside the largest vessels on the nerve at the site of injury. Within the next few minutes the groove filled out, the pallor disappeared, and no further hæmorrhages occurred. The intensity of blow used was not such as to induce hæmorrhage *within* any nerve bundle except in some control experiments in which hæmorrhage within the perineurium was especially sought. An instrument with more rounded edge had to be used to produce this effect. The wound was then closed aseptically and the animal observed daily for evidence of impairment of movement or sensation. Before sacrifice the wound was re-opened under light nembutal anæsthesia and the nerve stimulated above and below the damaged region. The animal was then killed, the nerve fixed in formol-saline and stained by osmic acid, Gros-Bielschowsky method, cresyl-violet, Sudan III, Spielmeyer's myelin stain, iron hæmatoxylin and other methods.

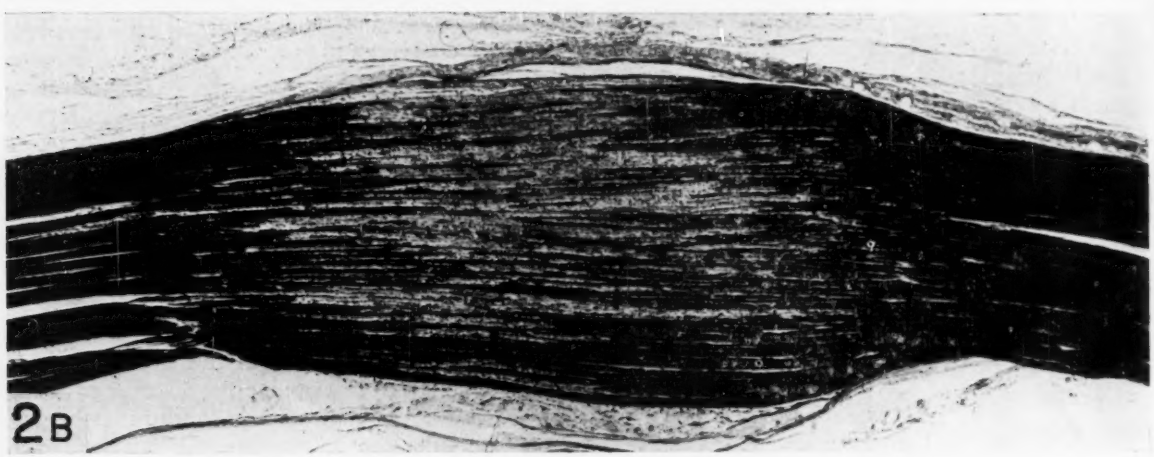
Findings

1. Persistent Paralysis

Percussion of nerve sufficient to impair conduction in some degree is followed by the appearance of a swelling (pseudo-neuroma) of the region of percussion (Fig. 2). If the percussion is so light that no disturbance of motor function is demonstrable, a few fibres in the nerve may be later found to have been damaged, but no swelling occurred in these circumstances in any of five experiments. It is convenient first to examine the disorder produced by a degree of trauma sufficient to lead to immediate loss of conduction of movement persisting for six weeks or longer, with Wallerian degeneration below the lesion. The changes were identical whether small hæmorrhages had occurred at the time of injury or not. If rupture of the perineurium occurred, additional changes appeared and these will be described in a separate section. Motor paralysis below this type of lesion was complete, but some reaction to a pinch of the pads of the toes always remained and in one experiment to a touch, showing that some pain conduction and sometimes touch conduction also was intact. Detailed observations on sweating and temperature were not made, but no gross change was observed.

Histological examination of the nerve within the first 24 hours after a severe degree of injury failed to demonstrate any change in the myelin or axis cylinders. Twenty-four hours after the injury the injured region of the nerve was swollen and œdematous. The myelin sheath of each fibre was greatly swollen throughout the œdematous region and the myelin irregular. Within three days most of the myelin at the level of percussion and for a distance of one or two millimetres above and below had disappeared. Large numbers of phagocytic histiocytes, containing fat granules, filled the œdematous endoneural spaces. Some vacuolar masses, staining faintly with fat stains, adhered to remnants of





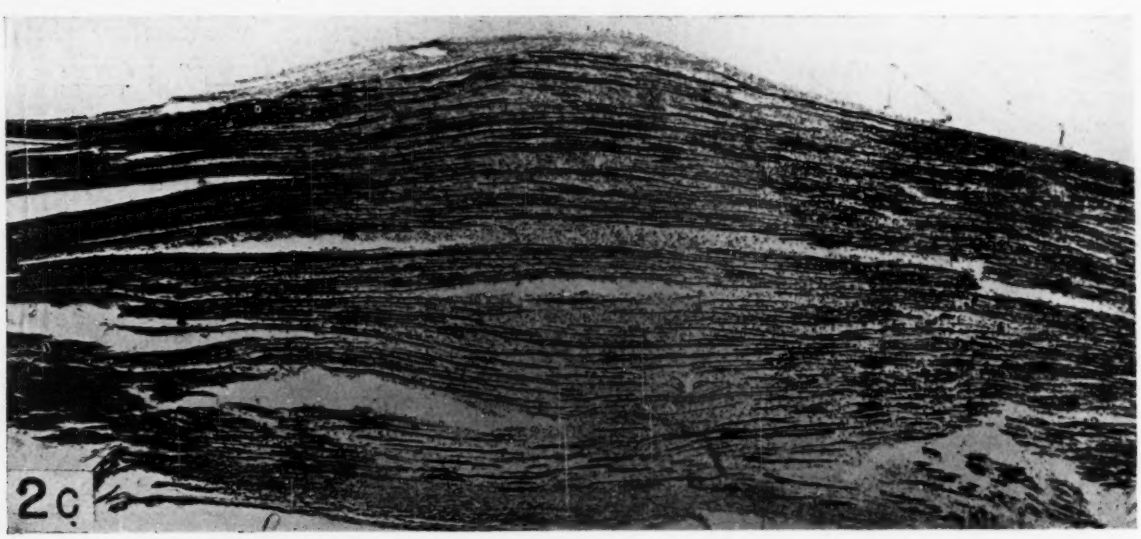
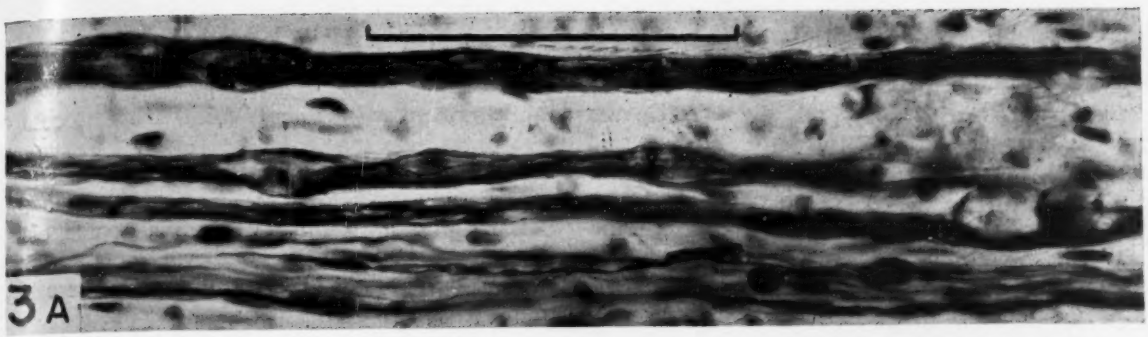
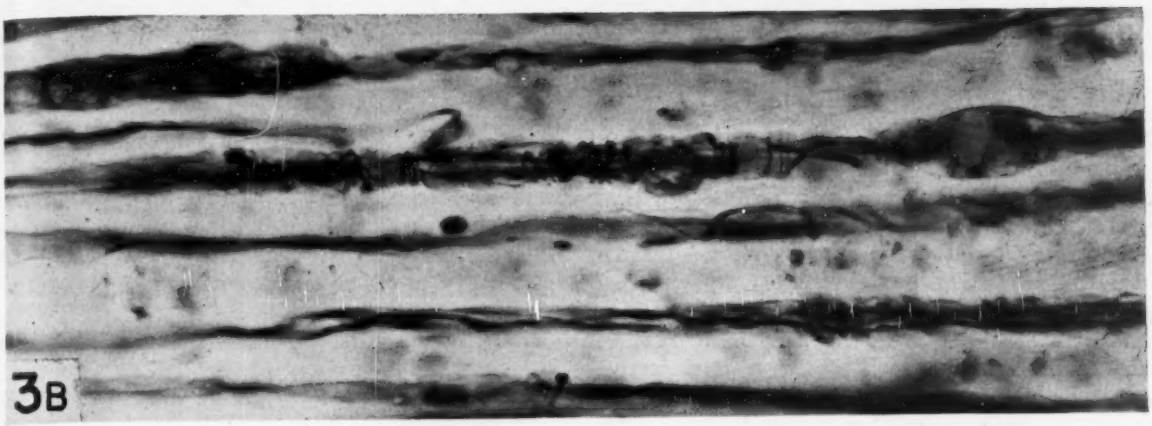
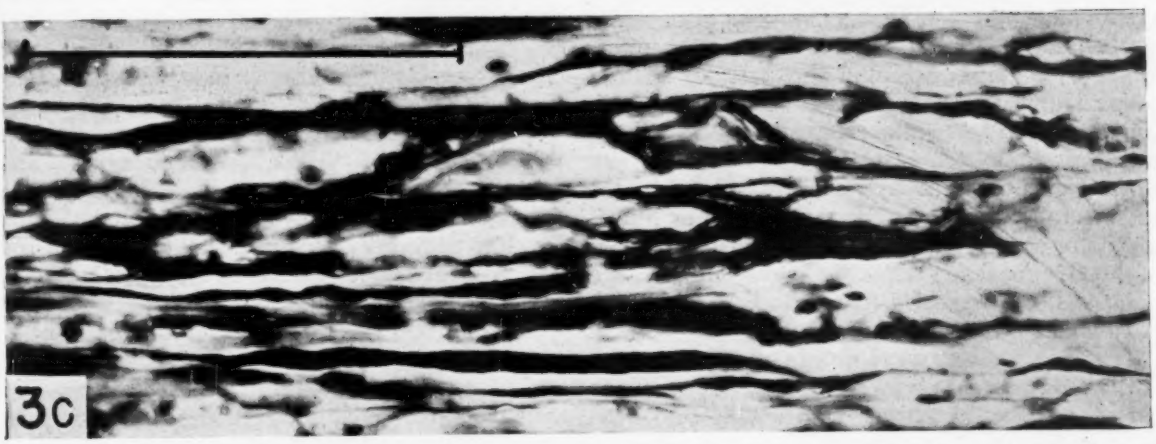


FIG. 2A.—Longitudinal section through the pseudo-neuroma, popliteal nerve, 13 days after injury. Complete motor paralysis, with sensation to pinch and touch persisted from time of injury. Electrical excitability of peripheral motor branches of the nerve was completely lost. Spielmeyer's stain for myelin. The left of the figure is proximal and right distal in all figures of longitudinal section. The ruled line in upper corner is equivalent to 1·0 mm.
FIG. 2B.—Popliteal nerve, 13 days after injury. Great weakness of plantar flexion for three days with preservation of sensation to pinch or touch throughout. Spielmeyer's stain. Magnification as in A.
FIG. 2C.—As 2B, Gros-Bielschowsky method for axis cylinders.







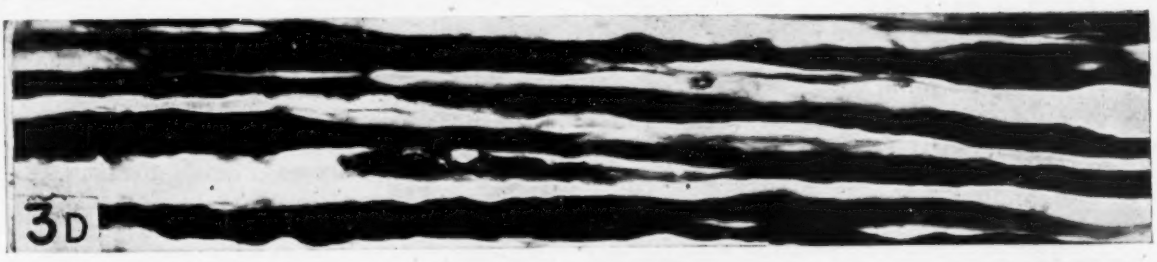


FIG. 3A.—Bundles of regenerating fibrils in the centre of the pseudo-neuroma, same experiment as 2A, 13 days after injury. Gros-Bielschowsky method, counterstained Sudan III and hæmatoxylin. The ruled line at the top of the figure is equivalent to 0·1 mm.

FIG. 3B.—As 3A, to show detail of branching of parent axis cylinder. The uppermost fibre loses the myelin sheath between the left and middle thirds of the figure. The remaining fibres are unmyelinated. Magnification is as in A.

FIG. 3C.—Axis cylinders just proximal to the level of percussion which begins at the right of the figure, three days after injury. Gros-Bielschowsky method. The ruled line at upper left corner is equivalent to 0·1 mm.

FIG. 3D.—As 3C, axis cylinders just distal to the level of percussion. Magnification as in C.

FIG. 3E.—Beading of non-medullated fibres 13 days after severe percussion. Gros-Bielschowsky.

the Schwann tube. The axis cylinders were greatly swollen, with irregular gaps and distortion in the proximal part of the œdematous area (Fig. 3C) and more regular expansion in the distal swelling (Fig. 3D). At the point of percussion all the larger axis cylinders ended in large bulbs or knobs, in the manner clearly described by Cajal (1928) in his account of trauma to nerve by pinch with forceps. For a millimetre above this, the axis cylinder had sprouted long leashes and whorls of fine fibrils (Fig. 3C), many of which had already forced their way into the empty Schwann tube for a millimetre or more. Others appeared to splay out into the endoneural spaces. Many of the finer axons were simply beaded and irregular in calibre as they passed the percussed region. Distal to the percussion the myelin and axis cylinders showed only the earliest signs of Wallerian degeneration.

Fourteen days after the injury such a nerve was invariably swollen at the site of injury, sometimes to as much as twice the diameter of the trunk above and below. The swelling consisted of a localized œdematous zone in which the nerve fibre strands were widely separated by fluid containing many histiocytes loaded with fat granules (Fig. 2A). The myelin had entirely disappeared in the centre of this swollen region, and the nerve fibres were represented by chains of Schwann nuclei in almost all of which multiple strands of regnerating nerve fibrils (Fig. 3A), and in the remainder a single axis cylinder, extended completely across the swollen region. These bands of fibrils lay relatively isolated by the endoneural œdema. Nuclear stains such as hæmatoxylin or cresyl violet showed the bands as bundles of nuclei traversing the œdematous region, and Laidlaw's stain revealed that each had a covering of endoneural reticulum.

Traced to the proximal myelin sheath the axon fibrils were found to spring from the stump of the old axon, either as a spray immediately below the last myelin or more commonly as the result of repeated sprouts from the old axon which was seen to run a variable distance as a pale unmyelinated single central core with sparse Schwann cells at intervals (Fig. 3B). Hæmatoxylin stains revealed an additional outer covering of scattered pale endoneural nuclei. At the point of division the axon was shrunken and stained darkly with silver. Few old axis cylinders passed the centre of the swelling and these branched before reaching the peripheral zone of Wallerian degeneration. A puzzling feature of such proliferating fibrils was their frequent grouping around a larger central fibre which at first appeared to be the persisting original axon. When traceable into the distal segment of the nerve such large axons coursed irregularly around ovoids of degenerated myelin in the old Schwann tube. Close examination convinced us that this appearance of persistence of the original axon at the 14-day stage was due to early maturation of a main regenerative axonic sprout, and that even at this time the profuse networks and spirals of finer fibrils were in process of resorption, for though common at the 14-day stage they were rarely present after three weeks. This process of resorption also explained the frequent occurrence at 14 days of side branches lying outside the sheath of Schwann and directed proximally (Fig. 3A). Bundles of non-medullated fibres appeared either to be intact but with frequent oval swellings, as in FIG. 6F, or to be beaded and irregular where they passed the axis of the pseudo-neuroma (Fig. 3E). On close examination a number of the thinnest medullated fibres were found to run far into the œdematous area before losing their myelin which they regained after 0·2 to 0·5 mm. and coursed distally without Wallerian degeneration. Five of these were in the section shown in Fig. 2A, but are too small to appear in reproduction. Silver stains showed corresponding thin single conductors with associated sheath nuclei, but it was difficult to distinguish these from regeneration except in two instances where such an axon was traced into a small distal intact myelin sheath.

After two weeks the loss of myelin in general coincided with the extent of the swelling both proximally and distally (Fig. 2A). More proximally the myelin sheaths were irregular and swollen for a further 5 mm., with corresponding irregularity and swelling of the contained axis cylinders. This irregularity and swelling we have found associated with simple œdema of nerve (Denny-Brown and Brenner (1944*b*)) and regard it here as resulting also from œdema. The distal portions of the nerve were in Wallerian degeneration. The myelin and axis cylinders were partly broken up into the familiar ovoids. The heavy content of fat and large fragments of undigested myelin in the whole peripheral segment was in marked contrast to the fine intracellular droplets in the traumatic swelling, described above.

The perineurium was in places lifted from the nerve bundles by fluid containing fat-laden phagocytes. This perineural œdema was variable in degree and never intense. There was no evidence of migration of macrophages or fluid proximally or distally from the swelling. The swelling of the nerve in such a lesion was associated with a localized stasis and congestion of all the vessels in the area. In the region of the nerve just distal to the traumatic swelling the regenerating neurofibrils were seen to pass directly into the degenerating Schwann sheath, coursing irregularly round the obstacles provided by ovoids and fat droplets (Fig. 3A).

After twelve weeks, the swelling at the site of trauma still persisted but was slight in degree. In an experiment where severe weakness, with retained sensation only to a severe pinch, had persisted for 30 days, with full recovery of spreading of the toes delayed until the eighth week, full regeneration had occurred. The regenerated fibres had each a separate sheath of Schwann, with commencing myelination, both in the swelling and beyond. No Perroncito spirals remained in the traumatic swelling. As shown in the two upper fibres in Fig. 8A, a few very small spiral branches besides the

original conductor had become medullated. This was the exception and no other trace remained of the rich branching that was seen in the first two weeks. It is assumed that most of the young fibres are subsequently resorbed, for the nerve contained few more fibres than just above the lesion. The perineurium was not thickened and there was no epineural change. There was, however, a persistent increase in the oval endoneural cells, which in a section stained with cresyl violet or other nuclear stain was seen to be limited to the region of previous percussion, and to be only very slight in the previously degenerated peripheral segments of the nerve. Associated with this nuclear increase was an intensification of the endoneural reticulum as revealed by Laidlaw's stain. The whole disturbance was much less severe than that caused by crushing the nerve with a hæmostat at the same level, and the onset of recovery is earlier. The completion of final recovery is, however, about the same for both types of lesion.

A complete transverse lesion of nerve caused by percussion is therefore remarkable in the speed of development of a localized swelling at the site of trauma, the rapid removal of myelin from the region of swelling and the relative escape of non-medullated and a few finely medullated fibres. Regeneration is precocious, but once the distal segment of nerve is reached proceeds as after any other interruption with a fairly complete ultimate reconstruction of the nerve. An increase of endoneural reticulum and nuclei marked the region of previous trauma.

2. Transient Paralysis

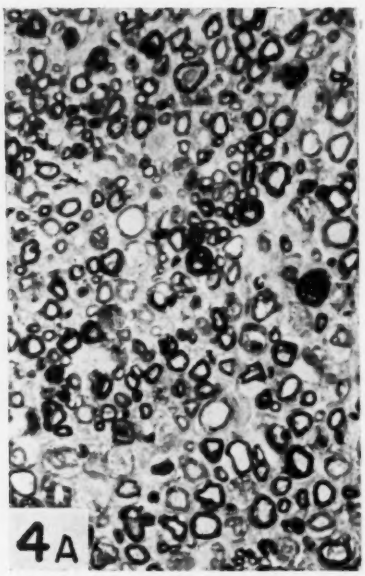
An intensity of blow sufficient to leave an immediately visible indentation on the nerve trunk and occasionally the appearance of a small pin point effusion of blood in the coats of one or more of the larger vessels in the nerve sheath may nevertheless not cause persistent paralysis. We have not attempted to measure the exact intensity of percussion causing such transient effects, for intensity depends on a number of factors which are difficult to determine, such as surface area struck and compressibility of the nerve. It was, however, found that within a wide range of intensities a light percussion would cause an immediate motor paralysis usually complete for dorsiflexion of the foot and spreading, and partial for plantarflexion, lasting three to four days, followed by rapid recovery in the next 48 hours. Spreading of the toes was always the most severely affected motor function in partial lesions and the last to recover in all lesions. There was no loss of sensation when the animal was first examined on recovery from anæsthetic 18 hours after the injury. The foot was even slightly hyperæsthetic to a light touch in the first three days. If pain sense appeared impaired in any degree, there was invariably also some persistent weakness, lasting more than two weeks. The nerve was explored, stimulated, and submitted to histological examination at varying intervals after the causation of this mild type of injury. Stimulation of the exposed nerve invariably confirmed the presence or absence of motor conduction as observed clinically, and, if the anæsthetic were sufficiently light, confirmed the maintenance of sensory conduction.

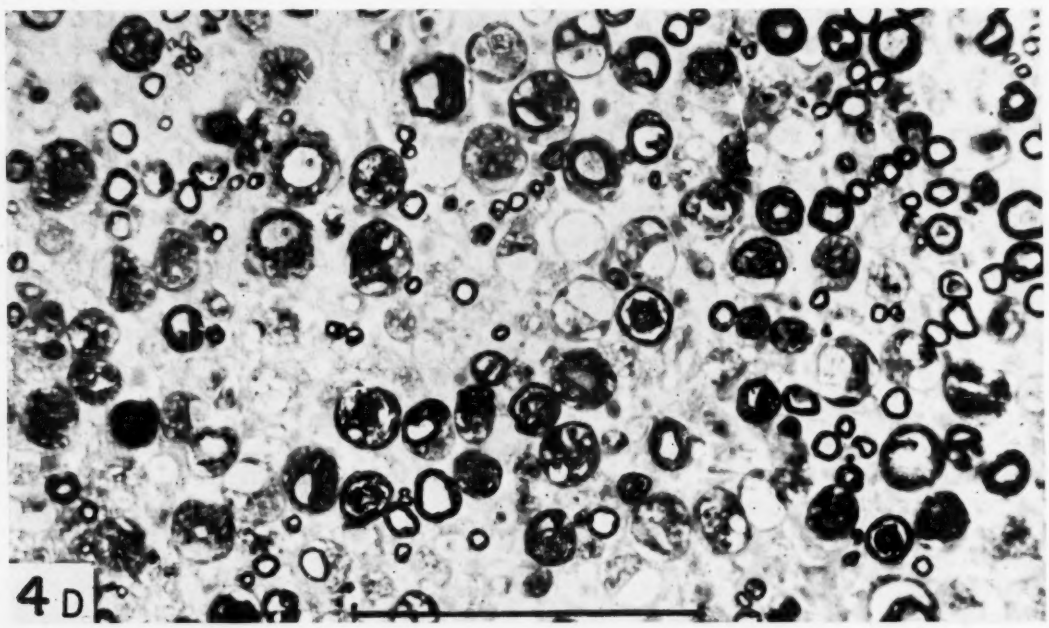
Three days after the percussion of the nerve a fusiform swelling had formed at the site of percussion, increasing the diameter of the nerve at this point to as much as 150 per cent. of normal. In very mild lesions the swelling was correspondingly slighter. This swelling was still remarkable after three weeks, and only just discernible after three months, in spite of early complete recovery of conduction. The swelling of "pseudo-neuroma" is due to interstitial œdema and the presence of large numbers of histiocytes in the widened endoneural spaces, in every way identical with that of severe persistent lesions. The œdema lifted the perineurium slightly at the height of the swelling. In the œdematous area the myelin of all large fibres had become greatly swollen and pale, and in some large fibres was in complete dissolution by the third day (Figs. 4A and B), leaving naked axis cylinders (Fig. 4C). The myelin of smaller fibres appeared to be unaffected in osmic preparations. Coarse, darkly staining fatty granules were seen in a moderate number of histiocytes which had appeared in the œdematous endoneural spaces.

Three days after the injury a few axis cylinders in each section showed the frayed appearance we have found to be general in severe, persistent lesions. The remainder were all greatly swollen throughout the pseudo-neuroma reaching diameters of 10 to 12μ as in Fig. 3D. At the point struck and for a short distance proximal to this the larger axons were distorted in a sinuous fashion, with intermittent pallor or failure of impregnation seen in some fibres in more severe lesions, as in the lower part of Fig. 3C. At either extremity of the pseudo-neuroma these swollen axons abruptly regained a swollen myelin sheath which became of normal appearance when traced a farther 1–2 mm. away from the lesion. Cell stains showed the presence of moderate numbers of histiocytes in the endoneural spaces at this stage and the oval, pale nuclei of the endoneurium were unduly frequent. The Schwann nuclei were distorted, but not otherwise changed. No mitoses of endoneural or Schwann nuclei were seen.

Transverse section of the swelling on the fifth day revealed myelin sheaths in all stages of disappearance at the level of percussion (Fig. 4D). The axis cylinder, unstained, or but slightly darkened in osmic preparations, was sometimes completely denuded of myelin, but more often had a crescent-shaped remnant applied to one side as in many of the unstained fibres in Fig. 4D. The residual myelin was swollen and pale except for small foci which were densely blackened by osmic acid. The nerve from which this figure was taken had shown clinical evidence of 50 per cent. loss of motor conduction for two days, with clinical improvement on the third day and no evidence of block of motor conduction on proximal direct stimulation on the fifth (last day).

These charges slowly became intensified. The





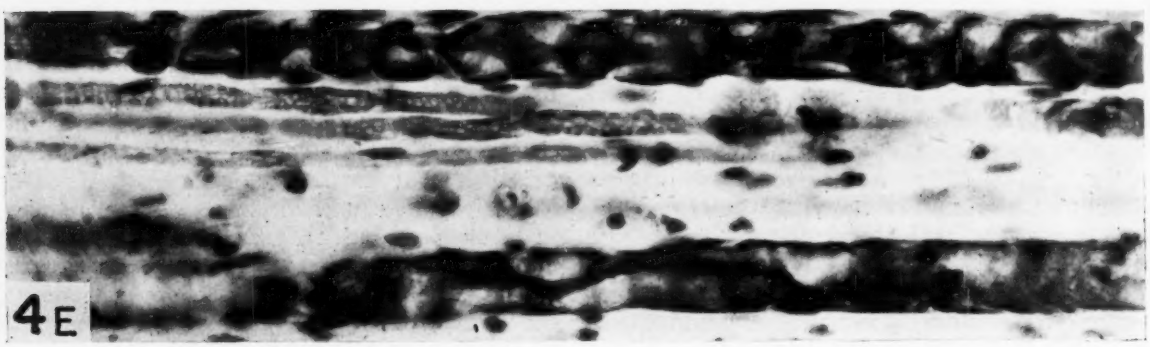


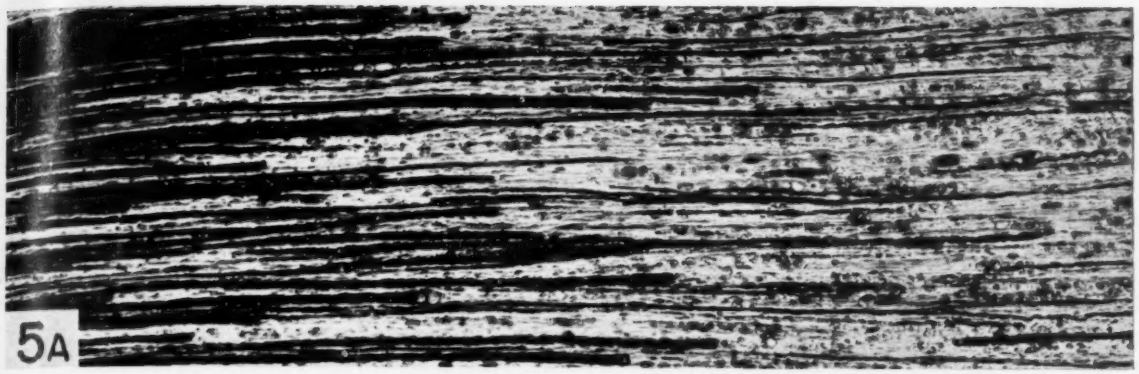
FIG. 4A.—Popliteal nerve. Transverse section of centre of pseudo-neuroma, three days after percussion. Complete motor paralysis until third day, sensation to touch and pinch intact throughout. Osmic acid.

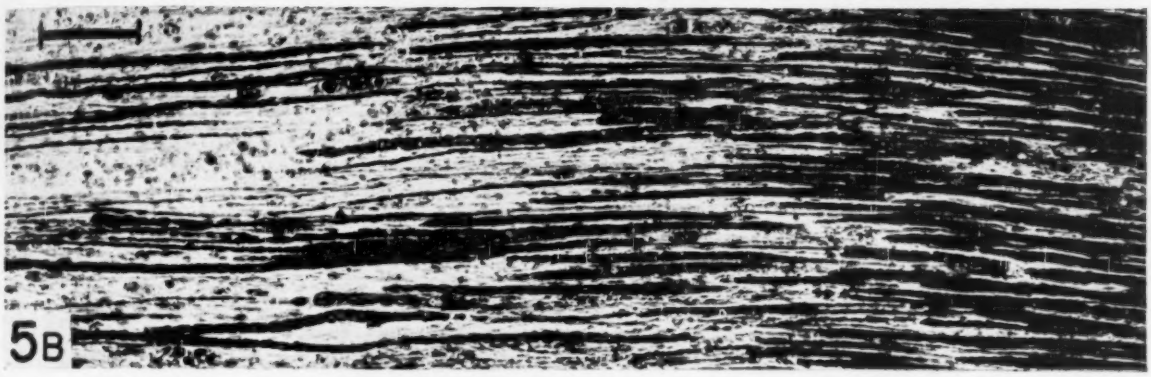
FIG. 4B.—As 4A, higher magnification.

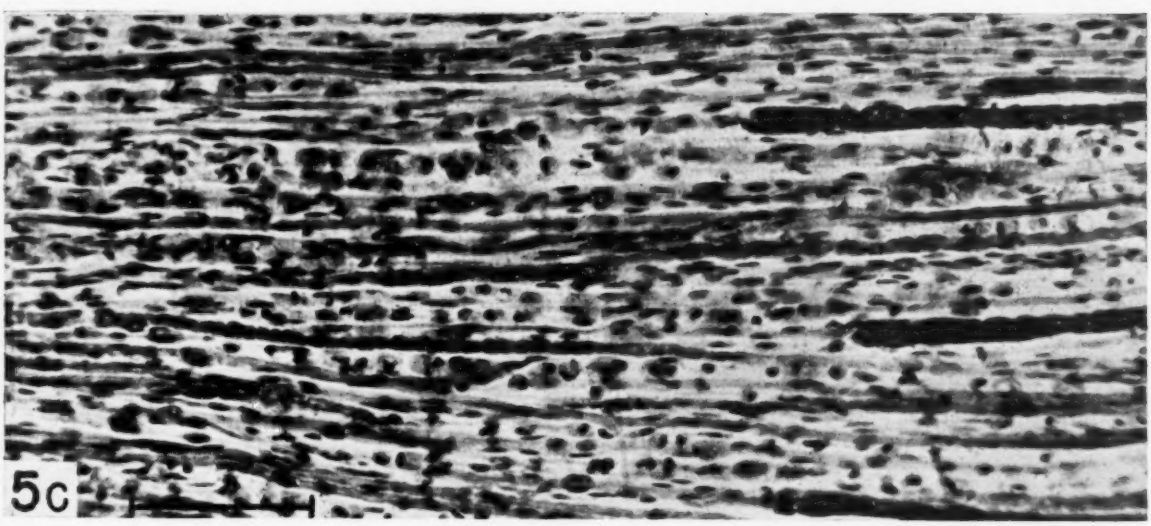
FIG. 4C.—As 4A, higher magnification.

FIG. 4D.—Peroneal nerve five days after percussion. Severe weakness of dorsiflexion of foot, paralysis of spreading recovering after four days. Sensation to pinch throughout. Osmic acid. The ruled line is equivalent to 0·1 mm.

FIG. 4E.—Peroneal nerve 13 days after percussion. Sudan III, to show two large and three small œdematous myelin sheaths near centre of pseudo-neuroma. The distorted axis cylinders of the large fibres are stained by hæmatoxylin.







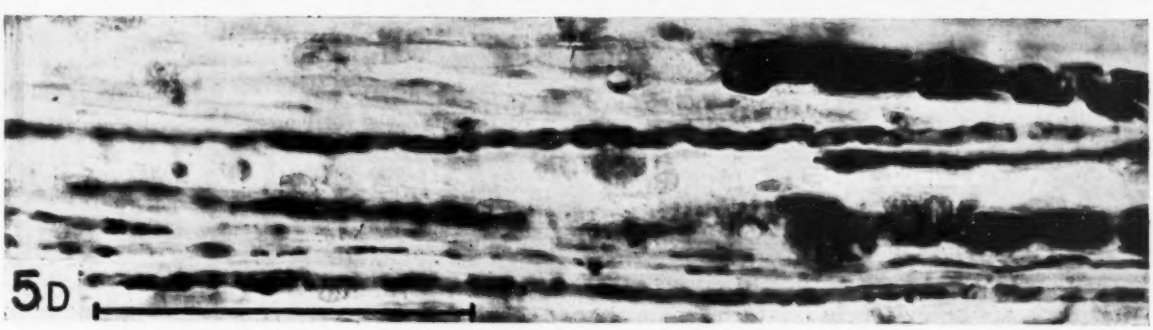


FIG. 5A.—Higher magnification of the proximal extremity of the pseudo-neuroma shown in Fig. 2B to show loss of myelin. Spielmeyer's stain.

FIG. 5B.—The same magnification of the distal extremity of the pseudo-neuroma in Fig. 2B to show recovery of myelin. The ruled line at upper left-hand corner is equivalent to 0·1 mm.

FIG. 5C.—Distal extremity of section of the same pseudo-neuroma to show recovery of myelin, small myelinated fibres and demyelinated axis cylinders. Sudan III hæmatoxylin. The ruled line in the lower left-hand corner is equivalent to 0·1 mm.

FIG. 5D.—Detail of recovery of myelin in two large and one small fibre (at centre), in the distal pseudo-neuroma shown in Fig. 2B, 13 days after injury. An extremely thin film of myelin covers the uppermost demyelinated fibre. Spielmeyer method. The ruled line is equivalent to 0·1 mm.

œdema and cellular reaction reached a maximum fourteen days after the original percussion. At this time axis cylinders appeared more widely separated and the phagocytic histiocytes more numerous (Fig. 2C). Occasional axis cylinders that had been interrupted now showed the plexiform branching with network of proliferated Schwann cells we have described in persistent lesions. These few bundles communicated directly with distal myelin sheaths that displayed commencing Wallerian degeneration. A few axis cylinders were swollen and irregular throughout the lesion but showed no irregularity in depth of staining with silver. The irregularity took the form of numerous projections, as in the large fibre near the top of Fig. 6B. By counterstaining frozen sections stained by the Bielschowsky method with Sudan (Oil Red O) stain for fat, these irregular swollen axons were shown to possess an intact though œdematous myelin sheath throughout the lesion. They were also clearly observed in Sudan sections counterstained with hæmatoxylin (Fig. 4E), and were evidently the "barbed" fibres of Tinel (1917). These intact fibres were present in inverse proportion to the number of degenerate (fibrillar) fibre bands. It was not found possible to obtain a pseudo-neuroma free from both. The bulk of the nerve fibres, however, were strikingly different, for the remaining 70 to 90 per cent. of axis cylinders stained unevenly with silver for a variable extent, and in the combined staining method many could be traced from the point when proximal myelin abruptly ceased to where the distal myelin abruptly recommenced (Figs 6A, B, C, D, and E). The demyelinated gap varied from 0·01 mm. to 1·1 mm. It was not possible to be sure of continuity of fibre in longer gaps which are suggested by sections such as that shown in Fig. 2B. In none of these was there evidence of distal degeneration of myelin, though for a distance up to 1 mm. on either side of the lesion the myelin was swollen and irregular. The peripheral nerve stained with osmic acid usually showed degeneration in fewer than 2 per cent. of fibres, and numerous sections of muscle failed to show degenerated end plates.

The demyelinated segment of axon was a single stout structure with limiting membrane and finely granular contents (Figs. 6C and D). There was always a cellular covering which was more distinct after the seventh day, partly owing to the separation of fibres by increased œdema, partly to collapse of the sheath of Schwann around the naked axon (Figs. 5C and D and Fig. 7). Two weeks after the percussion two types of nuclei accompanied the bared axons. At intervals of approximately 0·1 to 0·2 mm. the narrow darkly staining Schwann nuclei lay closely applied to the axon, usually indenting the surface (Figs. 6C, D and E and 7B). Schwann nuclei, normally distributed so that each one lies in the centre of a segment of about one millimetre, were redistributed between the seventh and fourteenth day so that one lay on the centre of each of the new, shorter and lightly staining, internodal segments. Various steps in this migration were observed, though mitosis was rarely seen. The young Schwann nuclei were smaller than normal, and had a high affinity for silver, so that in a lightly stained silver preparation only those proliferating nuclei may be stained (Figs. 6C, D, and E).

At similar intervals, but usually more numerous, oval, pale nuclei, lacking the nucleolus usually seen in the Schwann nucleus, lay wrapped around the fibre, often obliquely (Figs. 5C and 7A). Those were usually separated from the axon by a distinct interval, and in places the outline of a membrane could be seen between these pale nuclei and the Schwann nucleus (Fig. 7B). The pale oval nuclei were therefore interpreted as those of endoneural cells. They were readily distinguished from the more narrow pointed nuclei of fibroblasts. Their cytoplasm was rarely stainable and then appeared to be the fibrous endoneural reticulum of Laidlaw. With the Bielschowsky method the cytoplasm of the Schwann nucleus sometimes stains, giving a further differentiation from the endoneural nucleus (Fig. 7C).

The naked segment of axis cylinder did not show fibrillar change and did not branch in any specimen that could be traced into an intact distal myelin sheath. All axis cylinders that began proximally as a single core and more distally showed bifurcation or multiple branching (Fig. 3B) were, if traceable distally, found to enter Schwann tubes containing degenerated myelin. Lateral sprouts or branches were therefore always a sign of interruption of continuity. Proximal to the point of branching such an axon presented the same appearance as a demyelinated but uninterrupted cylinder.

Though increase in number of endoneural cells was observed on the third day the manner in which these cells embrace the demyelinated segment of axon is not clear until after the tenth day, when the Schwann sheath becomes more closely applied to the naked axon. The earlier distension of this sheath appears to be due to œdema and vacuolation. The endoneural cells did not embrace fibres which retained a myelin sheath (Fig. 7A). The penetration of the Schwann sheath by the phagocytic histiocytes, so commonly observed in Wallerian degeneration, was very rarely observed, and then only when some large myelin droplet remained in the Schwann sheath. The histiocytes remained in the endoneural spaces where they collected in large numbers (Figs. 5C, 6A, and 7A), their rounded cytoplasm filled with fatty droplets. Occasional lymphocytes and Mast cells were also seen. There was no evidence of migration of cells or œdema up or down the nerve. The blood vessels in the pseudo-neuroma were greatly congested (Fig. 7D) but showed no other change.

The smallest medullated fibres (2 to 3μ in frozen sections) appeared to escape demyelination in passage through the pseudo-neuroma. The myelin in these was often granular and poorly stained (Fig. 5D) by Spielmeyer's stain, but was intact in Sudan and osmic preparations. In the same figure the distal

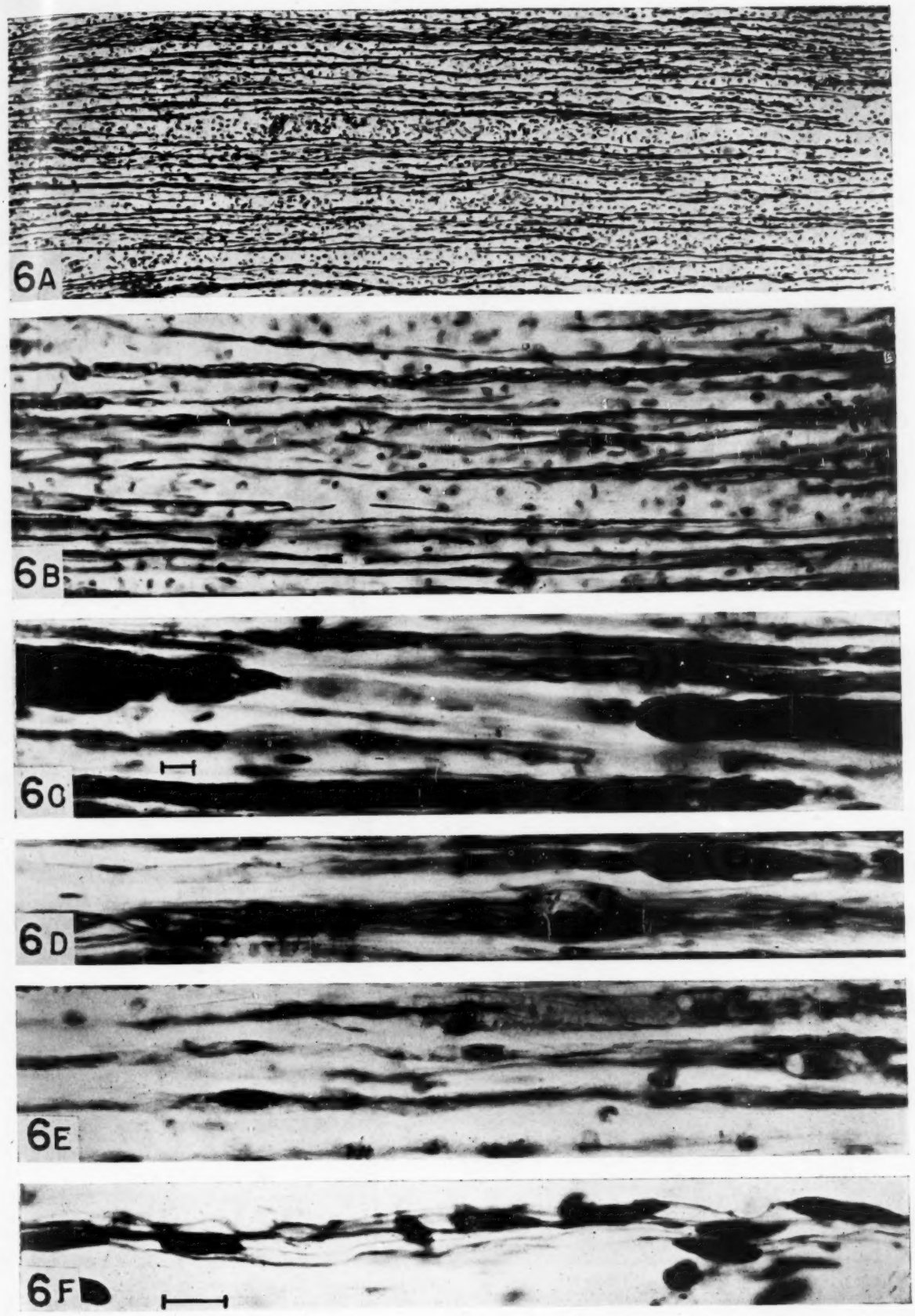


FIG. 6A.—Popliteal nerve. Centre of pseudo-neuroma from same nerve as shown in Fig. 2c, 13 days after injury, 10 days after recovery from severe weakness. Gros-Bielschowsky method.

FIG. 6B.—As 6A, higher magnification from another section, to show penetration of axis cylinder in œdematousmyelin sheath (second from top of figure), demyelinated and beaded axons.

FIG. 6C.—As 6A, to show short segment of demyelinated axon. Gros-Bielschowsky, Sudan III and hæmatoxylin. The small ruled line is equivalent to 0·01 mm.

FIG. 6D.—To show demyelinated axon joining the distal myelin sheath (above), and a regenerating bundle of fibrils (below).

FIG. 6E.—As 6A, to show junction of demyelinated axon with distal myelin sheath and two other naked axons.

FIG. 6F.—As 6A, non-medullated sympathetic fibres with normal Schwann nuclei and areas of oval expansion in the pseudo-neuroma. Gros-Bielschowsky. The small ruled line is equivalent to 0·01 mm.

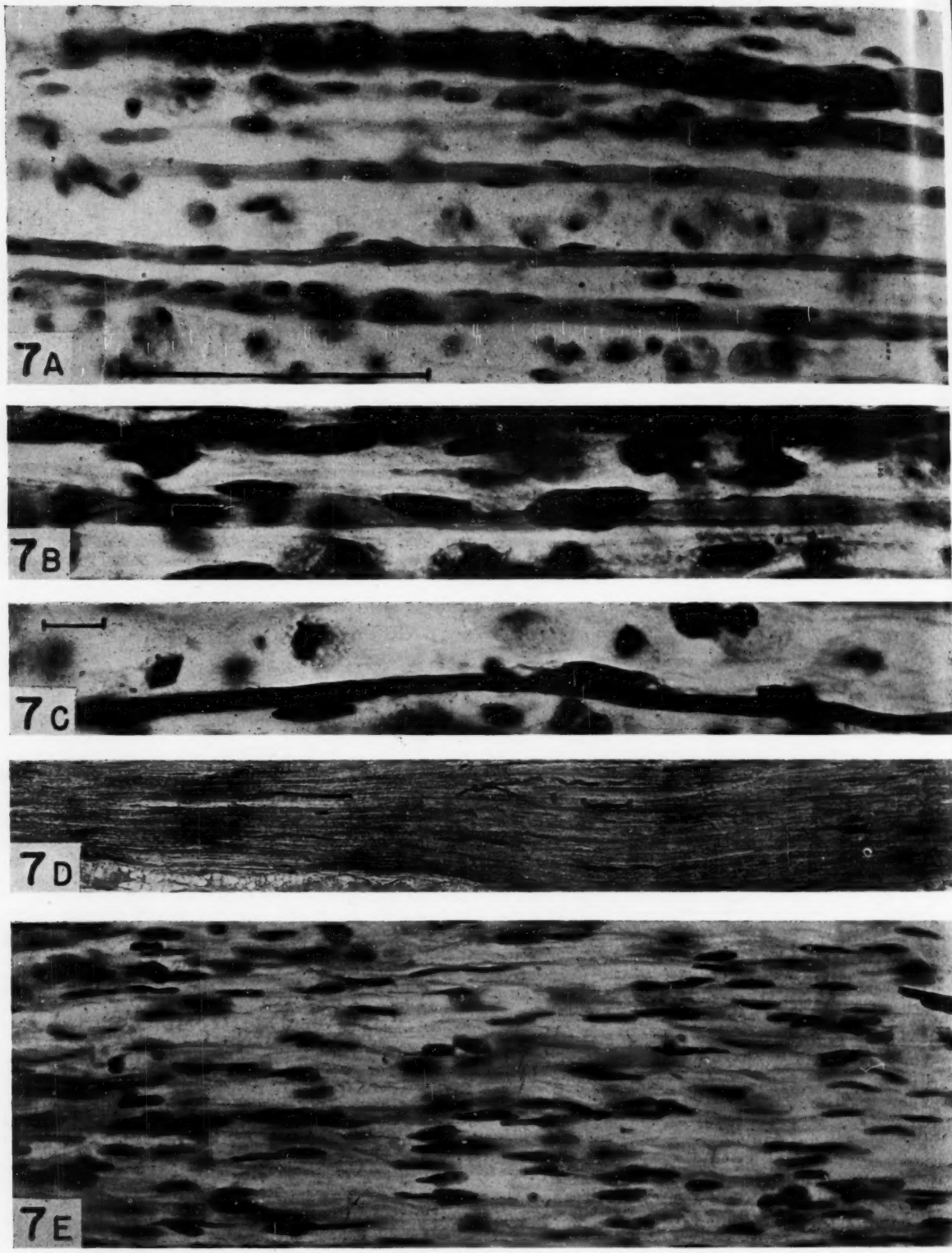


FIG. 7A.—Popliteal nerve as Fig. 5C, Sudan III, hæmatoxylin. To contrast the nuclear relationships of myelinated, but œdematous fibre (above), demyelinated naked axis cylinder (next below), finely myelinated axis cylinder, and Schwann sheath with regenerative proliferation (lowest). The ruled line is equivalent to 0·1 mm.

FIG. 7B.—High magnification of demyelinated axis cylinder. Sudan III and hæmatoxylin to show Schwann nucleus at centre with overlying membrane and endoneural nuclei to right and left clasped around outer (Schwann) membrane.

FIG. 7C.—To show cytoplasm of Schwann nucleus (to right of centre) in comparison with lack of staining of cytoplasm of endoneural nuclei (right and left). The ruled line is equivalent to 0·01 mm.

FIG. 7D.—Longitudinal section of region of percussion (to right of centre) three days after injury, to show congested vessels. Phospho-tungstic hæmatoxylin.

FIG. 7E.—Longitudinal section of region of percussion three months after the injury. Cresyl violet. To show persistent endoneural nuclei (pale) and normal distribution of Schwann nuclei.

end of the demyelinated segment of a moderately small fibre is shown. The demyelinated gap in such fibres was short, as can be seen in Fig. 5A where they are seen to run far into the œdematous area before losing myelin. Non-medullated axis cylinders appeared to cross the pseudo-neuroma intact, though oval formations were seen in the fibrils, probably an expression of œdema (Fig. 6F), as in severe lesions. Their Schwann nuclei remained intact.

3. The Formation of Pseudo-neuroma

Percussion, whether leading to rupture of axis cylinder or only to transient disorder of conduction, is associated with a precocious and localized breakdown of the myelin sheath. The process of slow ingestion of the myelin tube in the form of globules or "ovoids" by phagocytes, as seen in Wallerian degeneration, does not occur in the percussed region, but is replaced by a rapid dissolution of myelin, complete in three to five days. In that short period enormous numbers of fat granule cells with kidney-shaped or irregular nucleus appear in the tissue spaces, which are widely distended with fluid. The observed swelling of the nerve is directly related to this œdema. The vessels in the œdematous region are widely distended, but show no evidence of thrombosis. There is seldom any hæmorrhage into the endoneurium, and the swelling and other changes are independent of such occurrence. The histological picture is comparable with acute but localized inflammation. Polymorphonuclear leucocytes do not appear unless in relation to some small and adventitious hæmorrhage.

We found that if at the same exploration at which the nerve was percussed a tight silk ligature was tied 1 cm. or more proximal to the level of percussion all the phenomena of "pseudo-neuroma" could be produced, uncomplicated by the process of regeneration. Thus, three days after the percussion, all the myelin distal to the ligature was still intact and the axis cylinders swollen and irregular, except at the level of percussion. Here there had developed the usual localized swelling with endoneural œdema, and all myelin had disappeared (Fig. 8D). Numerous phagocytes filled the endoneural spaces. The axis cylinders of all sizes had broken into weakly staining fragments or had completely disappeared (Fig. 8E). On either side of the percussed region the axis cylinder was greatly swollen and frequently ended in a rounded, abrupt fashion. The Schwann cells had not proliferated. The appearance was consistent with a great acceleration of lysis and phagocytic activity.

In the course of previous work on compression of nerve (Denny-Brown and Brenner, 1944*b*) we have observed that the nerve on either side of a compressed area became œdematous and swollen. This change was related by us to vascular stasis. In moderate degrees of compression with dissociated block of conduction the œdematous reaction was also accompanied by a rapid dissolution of myelin and appearance of histiocytes, though these were absent in the œdema produced by minimal compressions not causing block. Guttmann and Medawar (1942) note the swelling of a nerve trunk above a ligature and state that such swelling does not develop if an additional ligature be tied 10–20 mm. proximally at the same time as the first, or if the proximal nerve be interrupted by the injection of chromic acid. These authors conclude that in the absence of nerve fibres, a swollen central end-bulb is not formed. Such experiments appear to us, however, to overlook other possibilities, for the vascular supply to the nerve between the ligatures or other obstruction was also abolished by their method. The same objection also appears to us to be inherent in the experiments of Weiss (1943), who, after slipping an arterial cuff over the proximal cut end of nerves, observed a larger swelling of the nerve proximal to the contracted segment of artery than distal to it, and concluded that the process of œdema then arose from obstruction of a centrifugal flow of endoneural and axonic fluids.

We have endeavoured to test these hypotheses by two sets of experiments. The effect of percussion of a section of nerve between two ligatures was examined with and without persistence of blood supply to the isolated segment. The ligatures were placed 10 to 15 mm. apart, and arranged so that in some experiments the isolated segment received the lower branch of the sciatic artery and vein, in others no blood supply. Without blood supply the isolated segment of nerve becomes shrunken and yellowish in colour in 14 days. There is some adherence to surrounding tissue. Percussion in the middle of the segment at the time of ligature had left no local swelling. Sections revealed only a uniform necrosis of all nerve structure. If the isolated segment were allowed to retain a blood supply from a branch of sciatic artery and vein it became somewhat swollen as a whole with greater swelling next each ligature. Percussion in the centre of the segment a few moments after the ligatures were tied had resulted in a small localized swelling at the percussed level fourteen days later. Within this swelling there was precocious disappearance of all myelin and axis cylinder remnants, and a localized intensity of histiocyte response with œdema. Further, if the proximal ligature was placed so that the nerve trunk received direct branches of sciatic vessels on either side the swelling occurred on the two sides of the ligature, perhaps more often a little less in degree on the distal side as Weiss has observed. Weiss concludes that the distal swelling is not œdema because the nerve fibres are not separated by fluid. We also found less endoneural fluid below the ligature, but we observed that the fibres themselves were more œdematous, being in process of degeneration.

The vascular supply to nerve trunks involves a longitudinal anastomosis between widely spaced tributaries, no one of which is essential for metabolism at any level. As we have recently described (Denny-Brown and Brenner, 1944*a*) ligature of pudic, sciatic and popliteal vessels to the sciatic

nerve in cats results only in patchy œdema without disturbance in function. The experiments described above, however, indicate that œdematous swellings related to ligature or other compression are greater when closely related to the entry of a vascular tributary, and we consider this to indicate that they are primarily derived from vascular factors.

The precocious disappearance of myelin in association with the localized œdema following percussion raises a further problem. The œdema requires an intact vascular supply. Is the œdema part of an inflammatory response to traumatic breakdown of myelin, or is the primary damage vascular and increased phagocytosis and myelin dissolution related to ischæmia ?

4. Percussion of Degenerated Nerve

We proceeded to degenerate the sciatic nerve by section between two ligatures, allowing the sciatic artery to give direct supply to the distal segment. After an interval of three weeks for degeneration, the nerves were re-explored and the distal-degenerated segment was percussed. After intervals of 3 and 14 days, the animals were killed and the nerves examined.

The effect of percussion of degenerated nerve was remarkable. Although no pseudo-neuroma was observed after intervals of 3 and 14 days, in frozen sections some slight increase of the œdema of the percussed region was present in comparison with the remainder of the degenerated nerve. The arrangement of macrophages and their general appearance was considerably changed in the damaged area. The change was most evident in frozen sections stained by Sudan III for fat (Figs. 9A and B). The macrophages were no longer vacuolated and compressed into the well-known " ovoids " of Wallerian degeneration, where the borders of one cell are difficult to distinguish from its neighbour. The macrophages in the percussed area instead lay free, with rounded cytoplasm filled with fat granules. The vacuoles had disappeared. The nucleus was larger and had lost the distortion typical of " foam cells." They had taken up an arragement in parallel lines, a re-arrangement that is obvious also in the bands of Bungner, which were also converted into parallel columns in the affected region (Fig. 9D) instead of the meshwork in which they contain Wallerian ovoids (Fig. 9C). Since this change was fully accomplished in three days and was confirmed in H and E, and Mallory phosphotungstic preparations, and since an occasional remnant of ovoid was rarely found, it was concluded that the macrophages had in fact been freed by the injury. All histologists have agreed that the macrophages present in Wallerian ovoids are " so compressed that the intercalary spaces are often obliterated " (Cajal, 1928). The source of this pressure has not been determined. The dramatic release of all the macrophages by a single sudden trauma indicates, however, that the Schwann tube, confining these phagocytes, was ruptured by the trauma, following which the macrophages came to lie in the endoneural space. The rapid disappearance of the characteristic vacuoles is also remarkable, and indicates that they are related to the previous tension. Whether the confining membrane is the neurilemma (wall of the Schwann tube) or an endoneural sheath is open to conjecture. We are in agreement with Holmes and Young (1942) that the neurilemma remains distinct in degenerated nerve, and in stained sections found no evidence that the endoneurium in such nerves confines the Schwann cell more completely than in a normal nerve.

Experiments on the effect of percussion of degenerated nerve therefore show that the effect of such trauma is then traceable to rupture of the Schwann tube. The " foam cell " then becomes an ordinary macrophage. The great œdema peculiar to a percussed normal nerve is absent. It is therefore concluded that the œdema and phagocytic reaction of the pseudo-neuroma is determined primarily by traumatic breakdown of myelin. From the appearance of splits in the myelin three days after percussion of normal nerve (Fig. 4B), and the remarkable decompression of phagocytes in degenerated nerve, it appears reasonable to assume that rupture of the neurilemma occurs in both instances by longitudinal splits, and that the tissue reaction in normal nerve is due to contact of myelin with endoneurium. Such rupture would also explain the precocious spread of leashes of neurofibrillar strands into the endoneurium and their later atrophy, an occurrence which at first we were at a loss to understand. It even appears possible that at the moment of the blow axis cylinder and myelin flow laterally through ruptures in the neurilemma.

5. Rupture of the Perineurium

In some experiments, immediately following percussion, a small white herniation appeared on the nerve at the point struck. This was likely to happen if the surfaces of the striking object and of the plate underlying the nerve were not parallel, so that the momentary compression of the nerve bundle was more to one side. The perineurium had ruptured and allowed nerve fibres to bulge through the opening. In such an experiment, where the peroneal division had developed such a hernia, the nerve was sectioned after 14 days' survival, paralysis of spreading and of dorsiflexion of the foot having been observed to persist, the swelling of the peroneal and popliteal divisions appeared to be that usually encountered. On section a proliferation of endoneurium, perineurium and nerve fibres through the opening was seen to have occurred (Fig. 10A and B). The spindle-shaped swelling on the peroneal nerve was partly a true neuroma. Myelinated fibres with irregular neurofibrillar regeneration bulged through the opening (Fig. 10A). The myelin in the remainder of the bundle was swollen and irregular on all fibres. Demyelination, leaving naked axis cylinders, was present in scattered fibres, throughout the unherniated portion (Fig. 10C) with a high proportion of regeneration. Though endoneural

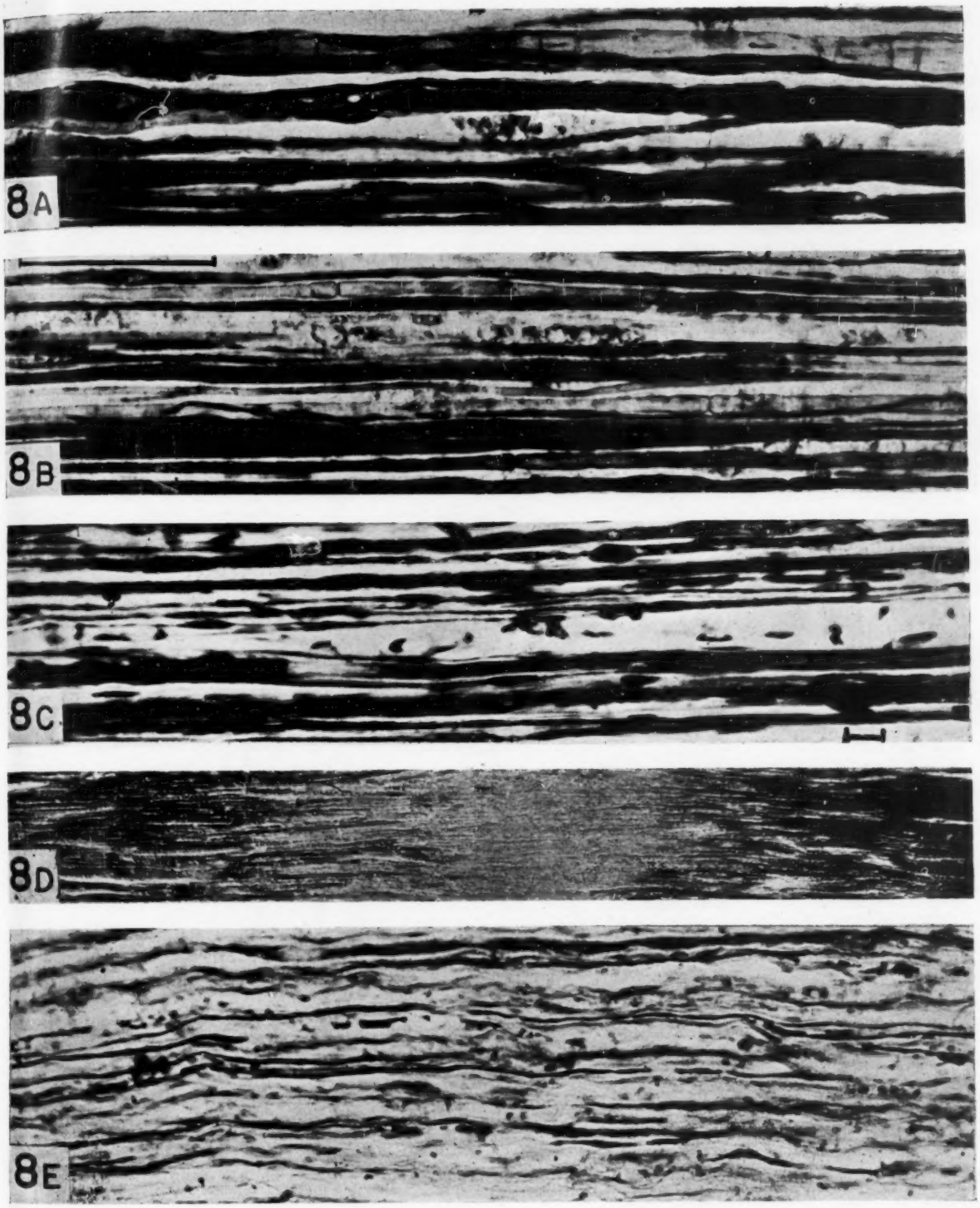


FIG. 8A.—Sciatic nerve at level of severe percussion three months earlier, causing severe paralysis for 30 days with complete recovery in 60 days. Spielmeyer's method to show very thin myelin sheath and small branches in uppermost fibre.

FIG. 8B.—Popliteal nerve three months after mild percussion causing partial weakness for three days, to show thin myelination at level of injury (no change distally). The ruled line is equivalent to 0·1 mm.

FIG. 8C.—As 8B. Gros-Bielschowsky method for axis cylinders to show irregularity of staining. The ruled line is equivalent to 0·01 mm.

FIG. 8D.—Popliteal nerve, percussed three days earlier and ligatured 2 cm. proximal to level of section. Iron hæmatoxylin. To show loss of myelin at level of percussion.

FIG. 8E.—As 8D. Gros-Bielschowsky method at level of percussion.

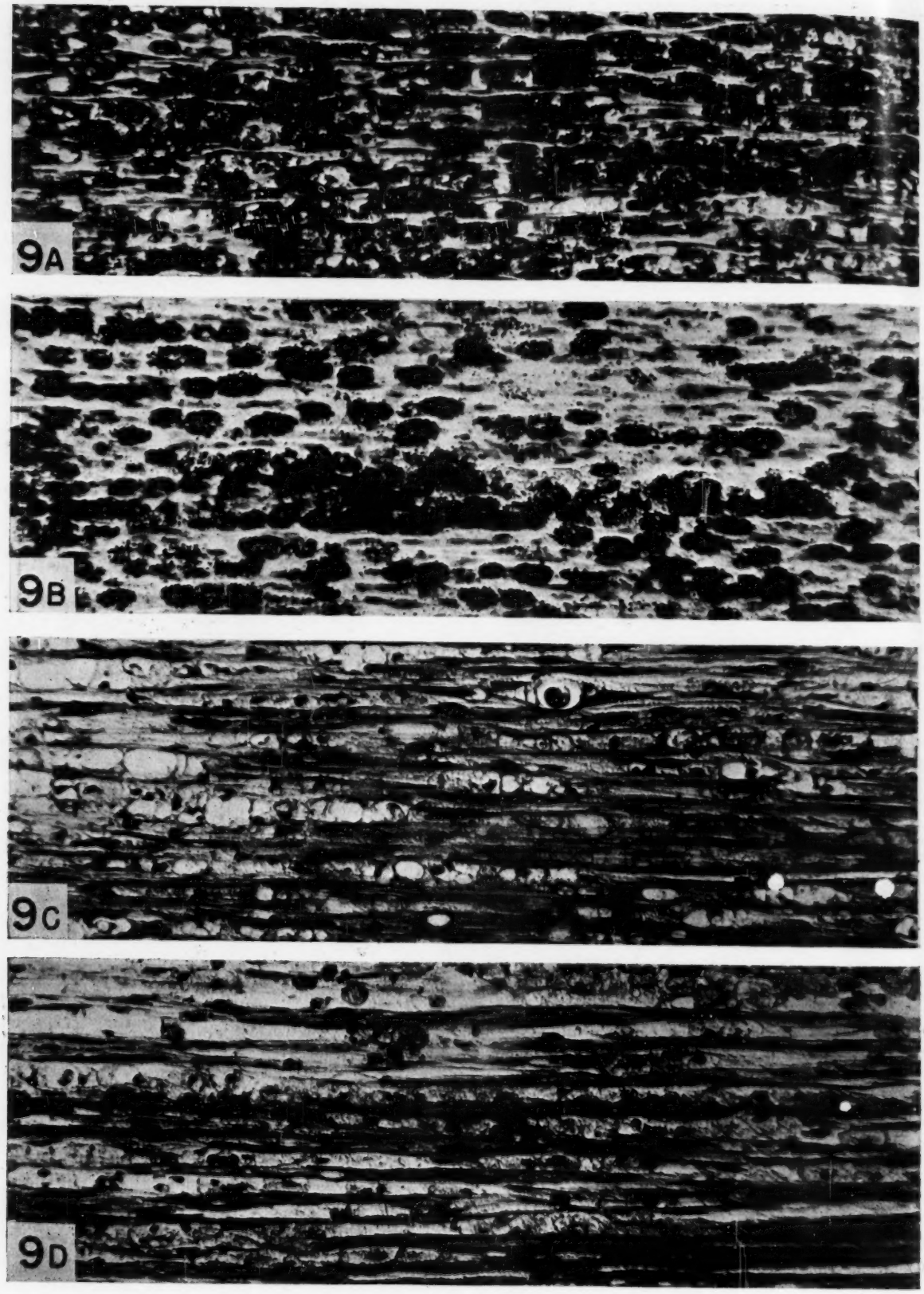


FIG. 9A.—Sciatic nerve, Sudan III, 24 days after section between ligatures 4 cm. proximal to region shown.
FIG. 9B.—As 9A, but 1 cm. farther distally, where the nerve had been percussed three days previously.
FIG. 9C.—As 9A, phosphotungstic acid hæmatoxylin.
FIG. 9D.—As 9B, phosphotungstic acid hæmatoxylin.

œdema was much less than in a pseudo-neuroma the naked axis cylinders were greatly swollen. Histiocyte response was present throughout the nerve at this level, but these cells were closely packed between the nerve fibres. There had therefore been spontaneous decompression of the perineurium. In other examples encountered it was observed that degeneration of all the fibres herniated through the opening and many of those near it had occurred by the fifth day. In one example, kept for six weeks, the proliferation of the hernia resulted in the formation of a large spindle-shaped mass with profusion of branching fibrils. There was still no evidence of recovery. Experiments of longer duration are in progress.

Discussion

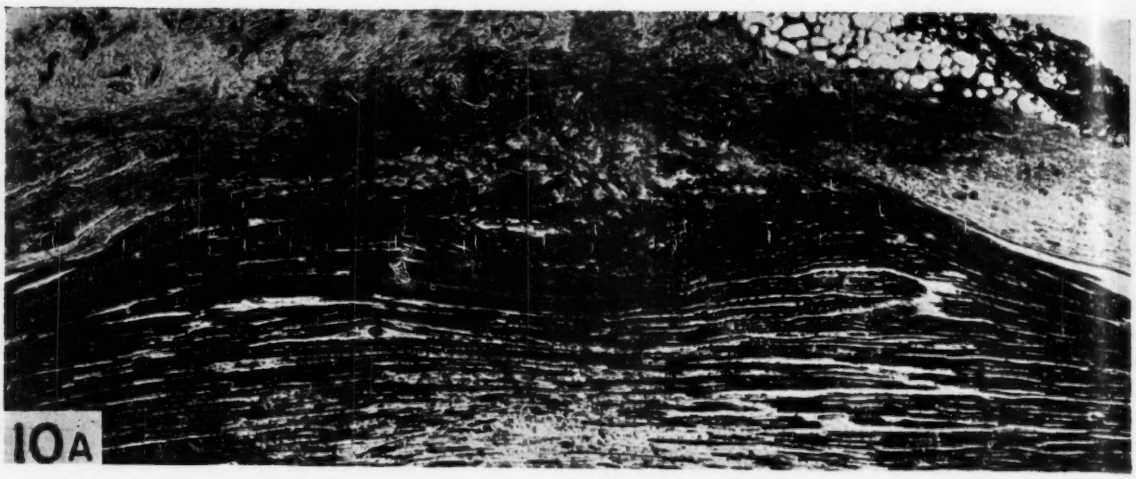
Percussion of peripheral nerve evokes a tissue response characterized by localized vascular stasis and œdema, with the appearance of large numbers of histiocytes and with proliferation of endoneurium. The myelin for a millimetre or more on either side of the level of percussion undergoes dissolution, and the histiocytes in the endoneural œdema become filled with fat droplets. This process is complete in three to five days. It differs completely from the chief histological feature of Wallerian degeneration, where phagocytes enter the sheath of Schwann and slowly ingest large globules or segments of myelin in the course of 2–25 weeks. Doinikow (1911), however, observed that in Wallerian degeneration some solution of myelin also took place, with the appearance of fat in surrounding endoneural cells and histiocytes. The rapid disintegration of all myelin by a process of solution following percussion is, however, sufficiently distinct to merit special attention. It closely resembles the rapid dissolution of myelin in a segment of nerve that has been frozen, as described by Bielschowsky and Valentin (1922). We have recently (Denny-Brown and Brenner, 1944*b*), described an identical dissolution of myelin consequent on compression of nerve, these being related to the effect of ischæmia under and immediately distal to the compressing agent. In that case there was also œdema and inflammatory response. In mild degrees the ischæmic lesion was associated with preservation of axis cylinders, and a block of conduction of motor fibres.

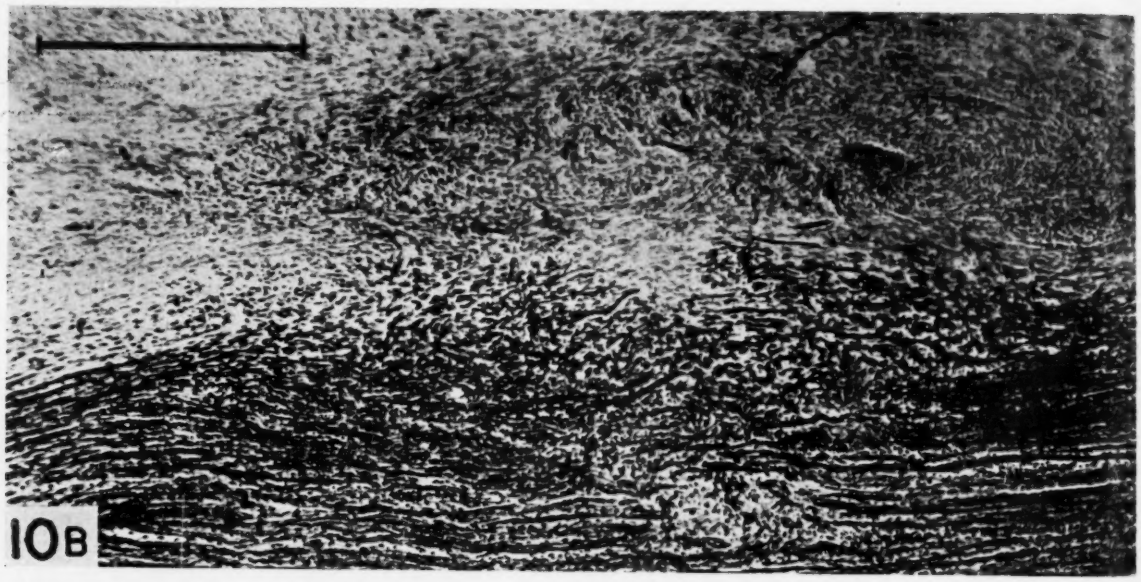
In the experiments here described a moderate degree of percussion led to localized disappearance of myelin without anatomical interruption of axis cylinders. Disturbance in function was then chiefly if not entirely related to motor conduction, and, though complete for three to four days, made rapid recovery. This milder type of lesion resembles the ischæmic lesion induced by compression, though it is of briefer duration. The possibility of a common mechanism in both compression and percussion lesions therefore arises.

Though percussion of a degree sufficient to cause impairment of conduction often led to some effusion of blood into the adventitia of the larger veins in the epineurium, these hæmorrhages are insignificant in relation to the remainder of the lesion and the changes described were independent of them. In other experiments, sub-perineural hæmorrhage, induced by gentle kneading, has in any case been found to be innocuous. No evidence of thrombosis of vessels was found early or late after percussion. All vessels in the affected area were greatly congested. If the perineurium was ruptured by the original injury the swelling or pseudo-neuroma was decompressed by the rupture, with herniation of endoneurium and nerve fibres through the tear. The damage to the myelin and the cellular response, however, still occurred throughout the nerve, though not to the same extent. The naked axis cylinders were then greatly swollen. Demyelination therefore does not depend directly on the internal pressure developed by œdema confined within intact perineurium, though it was less extensive when perineural rupture had occurred, nor does spontaneous decompression prevent the appearance of the fibrillary regeneration of some fibres throughout the nerve bundle. Lastly, whereas compression of nerve affected all sizes of nerve fibres alike (Denny-Brown and Brenner, 1944*b*), the demyelination from percussion was in all but the most severe degree selective for the largest myelinated fibres.

Escape of some of the largest fibres from demyelination, as in Fig. 2B, was related to slight asymmetry of the lesion, for they then lay to one or other side of the nerve bundle. In general we were satisfied that in the percussion lesion the measurable extent of demyelination in any given fibre bore a relation to the size of fibre, and was thus longest in the largest fibres. In ischæmic lesions the demyelinated gaps were by contrast surprisingly uniform in length (Denny-Brown and Brenner, 1944*a* and *b*). The ischæmic lesion also lacked the Schwann cell proliferation which was a late feature in the percussion lesion, and the demyelinated axon stained less well with silver. The essential nature of the percussion response, however, appeared to be the same in all kinds of medullated nerve fibres and varied only in extent. Non-medullated nerve fibres often presented a beaded appearance in passing through a pseudo-neuroma, but this in some specimens was the result only of a series of oval swellings on each such fibre, and was sometimes seen in fine medullated fibres. It is possibly only an expression of œdema.

The finding of preservation of sensory conduction, even to light touch in one experiment, where no myelin was found to pass continuously across the pseudo-neuroma, indicates that the dissociation of conductile function was not merely the presence or absence of demyelination. The rapid recovery of function, in spite of persistence of the histological change, also warns against close identification of loss of conduction with loss of myelin. We have already indicated a similar discrepancy in ischæmic lesions. It was notable that the transient motor paralysis, when partial, was more complete for distal muscles (spreading), a feature which is probably related to the finding in partial lesions in human





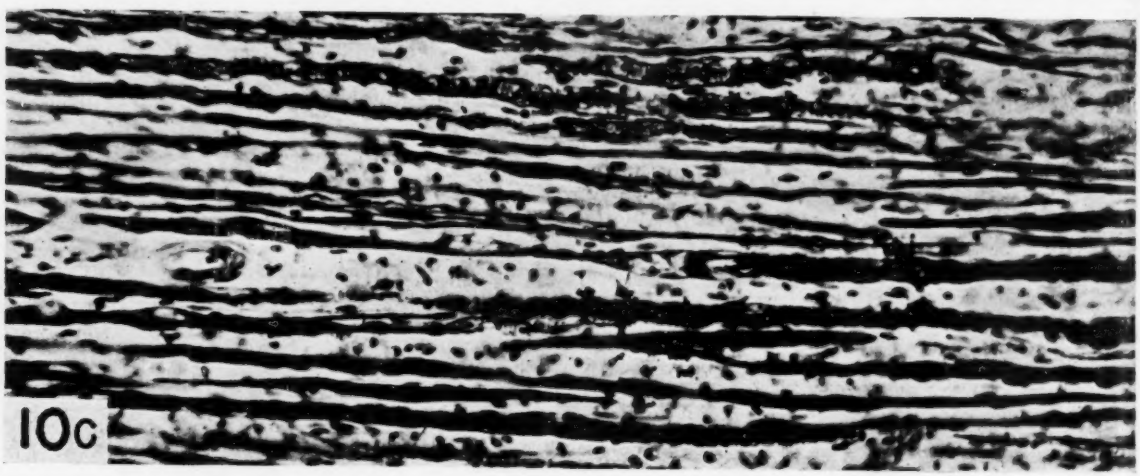


FIG. 10A.—Peroneal nerve at midsciatic level. Percussion with herniation through perineurium 12 days earlier. Spielmeyer's method for myelin. To show the herniation and decompression.
FIG. 10B.—As 10A. Gros-Bielschowsky method. The ruled line is equivalent to 0·5 mm.
FIG. 10C.—Fibres in the centre of the nerve in 10A stained by Gros-Bielschowsky method.

nerves that the proximal muscles may recover rapidly, the distal only after long delay or not at all (Claude and Dumas, 1917, Platt, 1921). Though it is tempting to relate such disturbance to selective effect of fibre size the evidence is lacking at present.

Seddon (1943) has recently introduced the term *neurapraxia* to describe disturbances in which paralysis occurs from a nerve injury which does not result in peripheral degeneration. The transient disturbances of function following percussion of nerve fall into this category. On account of the differences between the transient disturbance produced by percussion, and that of ischæmia or compression, we prefer to use the term neurapraxia for the clinical phenomeonon in cases of nerve injury when the actual mechanism is unknown. We have also avoided the use of the term *contusion*, for this implies the presence of extravasated blood, which is not an essential part of the percussion lesion. We have in fact been able to demonstrate that intrafascicular bleeding does not disturb function, if produced by kneading or other gentle physical manœuvre. The red blood corpuscles are hæmolysed and rapidly absorbed.

The initial mechanism of stasis and histiocyte response requires explanation. The almost complete absence of additional œdema and cellular change following percussion of degenerated nerve, and the striking mobilization of the histiocytes then already present, led to the conclusion that percussion led to rupture of the sheath of Schwann. Longitudinal continuity of the Schwann tube was retained, so that such rupture must therefore have been a longitudinal splitting. The argument is also applicable to the immediate disturbance of intact nerve by percussion. Splits in the myelin and Schwann sheath were observed on the third day. The breakdown of myelin is stated to release powerful tissue irritants such as cholesterol and thus induce stasis and histiocyte response in the central nervous system (Marsden and Hurst, 1932). This irritative phenomenon in peripheral nerve can also be related to breakdown of myelin by rupture of the Schwann sheath. Some of the bizarre bulbs, sprays, and side-branches of the axis cylinder which lie in the endoneurium at the level of a severe percussion may also represent herniations of the axon through the Schwann sheath at the time of injury. Like acute inflammatory reactions in other tissues the stasis and histiocyte response fail to appear in the absence of an intact blood supply. We have presented evidence that the fluid is not derived from any circulation of normal endoneural fluid, and once present does not migrate proximally or distally.

We have found the " barbed " axis cylinders and fibrillary cords described by Tinel (1917), and recognize the former as œdematous fibres still retaining myelin, the latter as regenerating fibrils. We have in addition described the truly demyelinated but otherwise intact axis cylinder, the survival of which is associated with brief block of motor nerve impulses. The lesion is never as pure as the compression lesion. A small proportion of degenerated fibres, and a larger proportion of intact myelination, is always present. An initially complete paralysis was associated with some degeneration, an incomplete paralysis with some unaffected fibres, but the number in each case was very small, and allows transient paralysis to be attributed to demyelination. It will be noted that the loss of myelin is apparent for two to three weeks after a four-day paralysis, and that the renewed myelin film was not observed earlier than the thirteenth day. We have noted this disparity between the slow process of remyelination and return of function in relation to ischæmic lesions also (Denny-Brown and Brenner, 1944*a* and *b*).

Apart from the œdema and tissue response pseudo-neuroma is distinguished from true neuroma by the parallel disposition of nerve fibres, whether they be the remaining " barbed " œdematous axons, the fibrillary bundles which betoken regeneration, or the demyelinated, single axis cylinders. This parallelism indicates that the sheath of Schwann has not ruptured transversely. If the axon is ruptured, regeneration occurs with great rapidity, associated with a profusion of secondary sprouts within the same sheath and proliferation of Schwann cells. Though most of the finer branches adopt a spiral course, the intricate spirals of Perroncito do not occur, and such lesser spirals as are seen are rapidly resorbed. Some branches run centripetally, and these already present resorptive knobs by the fourteenth day. The true Perroncito spiral is formed almost entirely of recurrent centripetal branches, indicating resistance to centrifugal progress. Further, though resorption of the interrupted axis cylinder is very rapid in the pseudo-neuroma (in three days following percussion below a ligature), one of the regenerative branches had frequently penetrated far into the peripheral nerve by the fourteenth day, and at the level of the pseudo-neuroma had already attained nearly the proportions of a mature axon. In contrast, a true neuroma presents essentially a confusion of direction of nerve fibres, which, with the persistent Perroncito spirals, indicates a transverse disruption of the sheaths of Schwann.

The œdema associated with pseudo-neuroma is accompanied by a brisk endoneural reaction. Though increase in number of the pale endoneural nuclei has been observed in simple œdema of nerve without damage to the nerve fibres (Denny-Brown and Brenner, 1944*b*), they are particularly clearly defined in relation to demyelinated but intact axons. The Schwann nuclei also proliferate, but to a less remarkable degree and at a later stage. Long after restitution of myelin the pale, oval nuclei of endoneural cells lie in the interspaces between the nerve fibres and mark the original site of the pseudo-neuroma. The endoneural cells are then presumably those that surrounded the naked axon in the acute stage of the lesion.

When the original lesion had been sufficiently severe to be followed by a paralysis lasting until regeneration occurred, a similar increase in number

of endoneural nuclei surrounds the fibrillary bundle of a regenerating axon in a pseudo-neuroma, and is then less obvious only because of the greater proliferation of Schwann cells. A persistent spindle-shaped swelling marked the site of percussion after as long as three months. The nerve fibre and sheaths were reconstituted (Fig. 8A), but occasional phagocytes and a large number of endoneural cells and fibres filled the dilated endoneural spaces. The phagocytes were fewer than in the degenerated peripheral segments. The tissue reaction is more intense than in the transient type of lesion. We were not able to identify additional fibroblasts. The traumatic neuroma of "traumatic ulnar neuritis" where trauma is repetitive, is likely to be the cumulative effect of repetition of either mild or severe degree of this process. The gross overgrowth in the endoneural spaces then strangulates the nerve fibres. Such a condition does not appear to arise as a result of a single percussion.

These findings throw some additional light on the phenomena of regeneration of nerve. They indicate that the phagocytic cells, which are attracted by degenerating myelin, are true histiocytes, probably derived from Maximow's "polyblasts" as Nageotte (1932) asserts. The "foam cell" appearance of the Wallerian ovoids is but another aspect of the same phagocytic "Kornzellen" (Doinikow, 1911) which lie free in the endoneural œdema. Neither is derived from the Schwann cell. Œdema of nerve is a characteristic result of trauma as in other tissues, and we find no evidence of migration of fluid or phagocytes either proximally or distally. It is difficult to concede the possibility of an endoneural or perineural circulation in the absence of such migration. The subsequent resorption of regenerative neurofibrillar outgrowths, excluding that that has been successful, is also clearly indicated. This phenomenon was suspected by Cajal (1928), and was clearly observed in the present experiments. It would appear desirable to investigate the influence of such abortive branches upon function of the conductor concerned, for such branching is the only histological evidence which suggests a clue to the phenomenon of hyperæsthesia. The behaviour of endoneural cells in covering the naked axis cylinders indicates a role previously confused with fibroblastic reaction. The phenomenon appears to have importance in the genesis of true neuroma, and demonstrates an essential difference between the endoneural cell and mesoblastic elements.

Rupture of the perineurium is an event which was more prone to occur if there had been asymmetry in percussion of the nerve, so that the momentary compression occurred more on one side than the other. Although the subsequent œdema was absent or greatly lessened, the histological and functional disturbance consequent upon such rupture was disastrous for nerve fibres near the resulting hernia. Nerve fibres, Schwann cells, endoneurium and perineurium proliferate through the gaping opening. There is formed a true neuroma with a characteristic tangle of fibres and cells. The neuroma may be lateral and single, or multiple, but fused to the fasciculus in such a way as to make it spindle-shaped. Except for some greater adherence to surrounding tissue it was usually indistinguishable from pseudo-neuroma to the naked eye. It was associated with great disorder of conduction of sensation and movement in some fibres for longer than six weeks, which is longer than the usual duration of paralysis from severe uncomplicated percussion at the midsciatic level. This delay in regeneration is related 'to the malalignment of Schwann tubes due to the perineural hernia, and to the great degree of lateral fibrillary and endoneural proliferation thus brought about. Even when the hernia is single and small the remainder of the nerve fibres in the nerve show the patchy demyelination characteristic of percussion lesion, with corresponding partial or complete block. All combinations between the pseudo-neuroma and multiple perineural herniation are therefore to be expected. This complication is likely to be the cause of late neuroma in cases such as that described by Maculaire and Navarre (1915), in which a projectile passed near the median nerve, but did not touch it, and yet a large neuroma resulted.

The descriptions of "spindle neuromata," found in association with prolonged partial disorder of function, and particularly with causalgia, suggests that multiple perineural rupture in the fasciculi which make up the nerve trunk may well be the mechanism of such residual disability. The disturbance of function associated with simple pseudo-neuroma was in contrast repaired extremely rapidly and effectively. We therefore suggest that, though repeated mild trauma may lead to permanent overgrowth of endoneurium, and consequent cumulative impairment of function, a single percussion of nerve can produce disorder in function lasting beyond the period of regeneration only through perineural rupture.

Conclusions

1. A single percussion of a nerve trunk resulted primarily in damage to the myelin sheath, probably with longitudinal rupture of the Schwann sheath and escape of damaged myelin into the endoneural spaces. The axis cylinder escaped interruption if the blow was moderate. Even in the most severe blows the axis cylinders of the finest medullated fibres and non-medullated fibres were not interrupted, and consequently did not degenerate. The sheath of Schwann was not divided transversely by intensities of blow sufficient to disrupt both myelin and axis cylinder.

2. A localized swelling or pseudo-neuroma developed rapidly at the site of injury and persisted for some weeks. The swelling was due to œdema, associated with the rapid appearance of large numbers of histiocytes. This reaction was related to the breakdown of myelin, and occurred if regeneration was prevented by a proximal ligature. It was prevented by interruption of blood supply.

3. In a moderate degree of lesion, when naked

axis cylinders of all sizes remained intact, there was retention of sensation with transient complete block of impulses in motor fibres. The smallest medullated fibres escaped or were less severely affected. Non-medullated fibres were then beaded but not interrupted. The dissociation in function closely resembled that caused by ischæmia, though hyperæsthesia to touch was more prominent, and recovery of motor conduction occurred more rapidly. Both the degree of œdema and extent of demyelination were lessened if the œdema was decompressed by concomitant rupture of the perineurium. Some ischæmia was therefore presumed to accompany the œdema and stasis, but was not an essential feature of the mechanism of the lesion.

4. The phagocytic reaction was derived from histiocytes. The Schwann cells played no part in the phagocytic process which was fully developed at the end of the first week when the Schwann nuclei began moderate proliferation along a demyelinated axon, or more profuse multiplication within the tube of a regenerating axon. The endoneural cells surrounded the isolated Schwann sheaths and remained in increased numbers even three months later when myelin structure was nearly completely reconstituted. This increase of endoneural cells was minimal in ultimate degree after a single percussion.

5. Transient paralysis lasting three to four days without loss of gross sensation was the effect of a partial lesion. A pseudo-neuroma was then also present. The majority of axis cylinders had lost myelin in passing through the lesion, but recovered it below. The extent of loss was greatest in the largest fibres. The characteristics of the demyelinated axon are described.

6. If the axis cylinder was transversely interrupted by the percussion, degeneration occurred in the distal portion of the nerve fibre. Regeneration was then extremely rapid (four to eight weeks) and complete. Such regeneration of axis cylinders in intact Schwann tubes involved an initial production of a large number of fibrils by the parent axis cylinder. Early maturation of one of these, presumably that which penetrated farthest, was followed by progressive resorption of the remainder.

7. Delay in regeneration resulted only when the perineurium was ruptured by the percussion. Herniation of nerve fibres and endoneurium then occurred, with true neuroma formation.

8. Percussion of a nerve trunk in process of Wallerian degeneration resulted in liberation of intratubal phagocytes (Wallerian ovoids). The phagocytes then assumed the characters of free fat granule cells. The mechanism of liberation appeared to be traumatic splitting of the Schwann tube.

References

Bielschowsky, M., and Valentin, B. (1922). *J. Psychol. Neurol., Lpz.*, **29,** 133.

Cajal, S. Ramon y. (1928). *Degeneration and Regeneration of the Nervous System.* Trans. by R. May, London.

Claude, H., and Dumas, R. (1917). *Bull. Soc. méd. Hôp.*, Paris, **33,** 626.

Dejerine, J., Dejerine, Mme., and Mouzon, M. J. (1915). *Pr. méd. No.* 31, 245.

Denny-Brown, D., and Brenner, C. (1944*a*). *Arch. Neurol. Psychiat.*, Chicago, **51,** 1.

—— (1944*b*). *Ibid.*, **52,** 1.

Doinikow, B. (1911). *Histol. u. histopath. Arbeiten v. Nissl-Alzheimer*, Jena, **4,** 445.

Guttmann, L., and Medawar, P. B. (1942). *J. Neurol. Psychiat.*, **5,** 130.

Holmes, W., and Young, J. Z. (1942). *J. Anat.*, London, **77,** 63.

Maculaire and Navarre (1915). *Paris. méd.*, **17,** 378.

Marsden, J. P., and Hurst, E. W. (1932). *Brain* **55,** 181.

Medical Research Council Special Report Series No. 54. *The Diagnosis and Treatment of Peripheral Nerve Injuries*, London, 1920.

Mitchell, S. Weir (1872). *Injuries of Nerves and their Consequences*, Philadelphia.

Nageotte, J. (1932). In Section V, of *Cytology and Cellular Pathology of the Nervous System*, Vol. I, edited by Wilder Penfield, New York.

Platt, H. (1921). *The Surgery of the Peripheral Nerve Injuries of Warfare*, Bristol.

Seddon, H. J. (1943). *Brain*, **66,** 237.

Tillaux, P. (1866). *Des Affections Chirurgicales des Nerfs*, Thèse de Paris.

Tinel, J. (1917). *Nerve Wounds. Symptomatology of Peripheral Nerve Lesions Caused by War Wounds.* Trans. by Rothwell, F., and Joll, C. A., London.

Tubby, A. H. (1915). *Brit. med. J.*, **1,** 57.

Weiss, P. (1943). *Anat. Rec.*, **86,** 491.

THE ELECTRO-ENCEPHALOGRAPHIC LOCALIZATION OF INTRA-CRANIAL NEOPLASMS

BY

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IT was first pointed out by Berger in 1929 that the presence of an intra-cranial tumour might cause changes in the electroencephalogram (e.e.g.), and since that time a considerable number of papers have been published which are concerned with various tumour effects and with methods for their localization. No recent paper has, however, discussed a fairly large series of cases, and this is my reason for adding one more to the number.

Technique.—The apparatus used was a 2-channel Grass ink-writing oscillograph, kindly loaned to this hospital by Professor E. D. Adrian. The use of only two channels for purposes of localization involves considerable difficulties, as well as expenditure of time, which are not present with three or more channels. Firstly, there is the simple point that more recordings are required to obtain equivalent coverage of the scalp; secondly, any given wave can be seen only in two positions, but ideally one should be able to study the distribution of any given potential change in as many positions as possible; thirdly, if amplitudes in three channels show a rising gradient, then it is probable that the origin of the disturbance is in the direction of the greatest amplitude, or, if the amplitude of the middle channel is lower than that of the outer ones, the disturbance probably arises between the middle pair of electrodes. Inferences of this sort are clearly not possible with only two channels, but the difficulty can be surmounted to some extent: 4 electrodes are placed in a row and recording is first done from 1–2, 2–3, and then from 2–3, 3–4; so long as 2–3 remains fairly constant in both recordings they can be regarded as approximately equivalent to a simultaneous three-channel recording. This point has been stressed because there appears to be a tendency in America for manufacturers to offer single channel oscillographs to the profession, and timely warning may prevent such misguided efforts here.

The routine recording was from four antero-posterior lines of four electrodes, low along either side and about 1 in. lateral to the mid-line: this was followed in some cases by similar transverse recordings, and then by odd placements according to the findings. Recording was bipolar throughout, the method being essentially that devised by Walter. The electrodes were saline pads on silver chloride-silver, in Perspex mounts. The patients were for preference seated, but when their condition did not allow of this, were lying on an earthed metal trolley.

The material for these investigations consisted of 155 consecutive suspected intracranial space-occupying lesions. Among the earlier cases there was some degree of selection by the clinicians, the e.e.g's. being requested more particularly in cases of doubt, so that, for example, very few pituitary tumours are included in the earlier part of the series; the later cases are consecutive and unselected. From the 155 cases, 30 have been rejected because either the exact nature or localization of the lesion remained in doubt, or the patient's unco-operative state prevented an adequate recording. The remaining 125 lesions were fully confirmed in site and pathology, though not in all cases in extent.

TABLE I

AGE	0–5	6–10	11–16	16–20	21–30	31–40	41–50	51–60	Over 60
No.	—	2	3	10	20	32	30	19	9

Distribution in Age Groups.

The sexes were fairly equally divided, with 69 males and 56 females. The distribution of age groups is shown in Table I.

Analysis of results

In Table II the lesions have been grouped partly on an anatomical and partly on a pathological basis. Of the 21 subtentorial tumours, only three were correctly lateralized. Although some claims have been made to localize cerebellar tumours by means of the e.e.g. (Smith, J. R., *et al.*, 1940), its usefulness in this sphere appears more than doubtful. On the other hand, the record commonly shows a generalized abnormality which may be of confirmatory evidence in conjunction with the clinical data.

TABLE II

	CONFIRMED 125						
	SUB-TENTORIAL 21					MENINGIOMATA 21	
	NEUROFIB.	OTHERS	MIDLINE — BASAL	GLIOMATA	ABSCESS	CONVEXITY	BASAL
TOTAL	6	15	18	62	5	15	6
NORMAL	3	2	2	4	–	3	2
ABNORMAL	1	11	14	16	1	4	1
LATERALISED	2	2(1)	–	9 (2)	–	–	–
LOCALISED	–	–	–	33 (6)	4	8	3

Analysis of Material. Normal—not definitely abnormal. Abnormal—but not lateralized. Lateralized —but not localized. Figures in parentheses—incorrectly lateralized or localized.

he second group, of midline and basal tumours, is a mixture of pituitary, 3rd ventricle, brain-stem, and similarly situated lesions, some benign and some malignant. Localization in the usual sense is clearly not possible, so no attempt has been made to tabulate results, but this does not mean that suggestive and useful evidence has not been obtained.

The remaining lesions are all cerebral, in most cases approaching or reaching the free convexity; with the gliomata it is, of course, difficult to be sure of the exact relationships and extent of the tumour. Because of their defined boundaries, and also clinical importance, the meningiomata have been grouped separately, with the exception of two posterior fossa tumours which are included in the subtentorial group. Abscesses affect the e.e.g. in a similar manner to tumours, but on account of their greater acuity tend to show more and slower electrical activity.

TABLE III

	NORMAL	ABNORM.	LATERAL.	LOCAL.	INCORRECT.
No.	9	22	7	42	8
%	10·2	25	8	47·8	9

Analysis of corrected results in 88 cases. 62 gliomata, 5 abscesses and 21 meningiomata.

Table III shows the results obtained from the 88 " cerebral " lesions which might have been expected to be susceptible to localization. It will be seen that approximately only half were correctly localized, a figure which is considerably lower than that of some previous writers. This is, no doubt, in part due to inexperience—the percentage is tending to rise—and in part to the disabilities imposed by the use of only two channels.

Alpha Rhythm.—No exact analysis of the distribution of alpha frequencies has been attempted, but in Fig. 1 the percentage of cases falling into consecutive frequencies from <8/sec. to>14/sec. has been compared with similar findings in 100 acute (less than 3 weeks) head injuries, 100 chronic (more than 3 weeks) head injuries and 400 mixed cases of all types, including epileptics, psychoneurotics, etc., but excluding tumours and head injuries. It will be seen that in the tumour cases there is a greater tendency to slowing of the alpha rhythm than in either of the other groups.

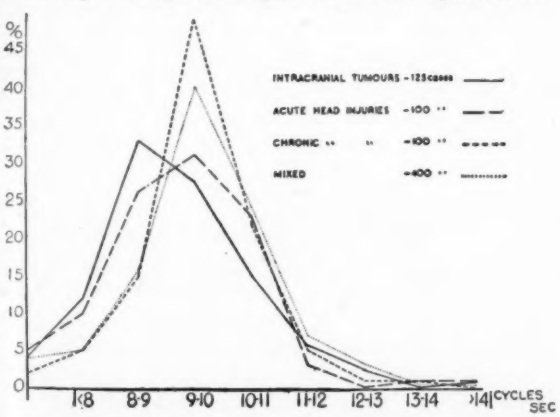

FIG. 1.—Distribution of Alpha frequencies shown as percentages of total in each group. There is a slightly greater tendency to slowing in the Tumour group than in either of the others.

Noticeable asymmetry of the alpha rhythm is not a very marked feature of the records, though at times it is a useful aid to lateralization. Assessment is sometimes complicated by unilateral overshadowing of the alpha rhythm by gross slow activity. Ten patients showed an alpha rhythm of lower voltage or lesser regularity on the side of the lesion, while in two patients the reverse was the case. One of the latter had an acoustic nerve tumour, and the remainder had cerebral hemisphere lesions.

Raised Intracranial Pressure.—As in the clinical picture of an intracranial space-occupying lesion, so the e.e.g. may be composed of at least two fractions: that due to high intracranial pressure and that due to local changes. Although in the majority of cases it is not possible to separate these two effects with any certainty, it is nevertheless tempting to surmise that certain generalized effects are due to raised pressure. High pressure, in this sense, is really a misnomer, because the effects are found to have little direct relation to observed pressures, and for the more cogent reason that it has been demonstrated (Williams, 1939) that the withdrawal of c.s.f. from the ventricles has little effect on the record, while dehydrating the brain by means of hypertonic solutions does bring about an approach to normality. In other words, the " high pressure " record is really one of cerebral œdema.

From the e.e.g. standpoint the " high pressure " record is probably seen in its purest form in posterior fossa lesions, particularly small mid-line tumours blocking the 4th ventricle or aqueduct: such tumours being unlikely to give rise to any local effect. Between this " pure " effect and that so frequently seen in conjunction with localizable cortical lesions, it is not possible to draw any line. Despite statements to the contrary I do not believe there is any characteristic feature of the " high pressure " record by which it can be recognized with certainty. The abnormal waves are generalized, usually uniformly so, they are slow, though not necessarily very slow; fast waves have not been noted to be of special significance. A range, in a single record, from <1/sec. to 7/sec. has been seen, but it is more commonly around 2–4/sec.; occasionally the waves have been rhythmic and more or less sinusoidal, but this is very exceptional and the usual impression is one of great irregularity. Amplitude is seldom very high and often less than that of the alpha rhythm.

As mentioned above, there is no direct correlation between the height of the c.s.f. pressure and the degree of abnormality of the record. One patient with a 6 weeks' history of blurred vision, and an initial c.s.f. pressure of over 300 mm. had a normal record. Nor does the presence or degree of papillœdema appear to bear much relationship

to the degree of abnormality of the record. There is greater correlation with the patient's state of consciousness, though even here the parallelism is by no means exact.

In general, in the absence of toxæmia or recent head injury, a record showing diffuse random slow activity of moderately high voltage is likely to be due either to "high pressure" or to cortical atrophy or vascular disease. The distinction is often possible on clinical grounds, but in cases of doubt it might be advantageous to apply Williams' technique of dehydrating the brain. I have not used the method for this purpose, but have found it satisfactory for separating high pressure from tumour effects in certain cases.

Local Effects.—These cannot be distinguished with certainty from the generalized effects of high pressure except by their focal or unilateral distribution, but high amplitudes and very slow frequencies are uncommon as pressure effects. The usual tumour record is a mixture of slow frequencies, sometimes quite haphazard, more often with one or more fairly regular frequency predominating, and sometimes occurring in well-defined bursts of almost sinusoidal form. Although perhaps it is true to say that the typical tumour record is one of very slow irregular waves of fairly high amplitude, the minimal appearance of only moderately slowed waves is not uncommon, and there is no feature by which their neoplastic causation can be forecast with certainty. Recent focal head injury, localized cortical atrophy, cerebral hæmorrhage or thrombosis and similar disruptive lesions may all produce the same type of record and distinction may not be possible on the evidence of a single recording: repetition at intervals, showing progression or regression of the electrical changes, will usually make the diagnosis clear.

In the common type of record in which there is a mixture of several frequencies, as opposed to a succession of completely irregular waves, it is sometimes possible to locate the separate origins of some of the frequencies; it seems at least probable that each frequency has a separate origin, rather than that the pace set by a common pacemaker is varied.

Localization.—The method of localization to be desired is the finding of phase-reversal of the slow waves, but this is by no means always achieved: 11 of the 62 gliomata were localized in this way, 2 of the 5 abscesses, and 7 of the 22 meningiomata. Although phase reversal gives the most definite indication of the source of the slow waves, this does not necessarily coincide with the site of the tumour, though it is usually in close anatomical association with it.

Walter (1937) has pointed out that in such cases an area of cortical œdema may coincide with the delta focus—in one such case phase-reversal occurred some 5 cm. posterior to the position of the tumour—and the clinical signs may even be associated with the œdematous area rather than with the tumour site.

Another not uncommon finding is that of a delta focus associated with a deep central lesion. The delta waves must be cortical in origin, the cortex either being deprived of control by deeper structures or driven by them at an abnormal rhythm. In one case a small glioblastoma of the posterior end of the corpus callosum gave rise to fairly regular 3/sec. waves with phase-reversal in the region of the inion, while another is recorded below:

Case 1.—D. S., a girl of 15 who had a six weeks' history of headaches, associated for the last two weeks with vomiting. At the time of admission she had her first attack, lasting 2–3 hours, of diplopia on looking to the left. There was nothing of significance in her past or family histories.

When examined she had: some stiffness of the neck, bilateral papillœdema with 3–4D of swelling, slight right external rectus palsy, some left facial weakness, hypotonus of all limbs with inco-ordination of the right arm and leg. The tendon reflexes were all diminished but symmetrical, and the plantar responses were flexor.

The e.e.g. findings (Fig. 2) were: (1) An 8/sec. alpha rhythm, largely masked by other rhythms. (2) A 2/sec. rhythm, tending to occur in fairly regular bursts of high voltage (150 micro volts) and showing phase reversal in both parasagittal parieto-occipital positions. It was temporarily inhibited by eye-opening. (3) A fairly continuous diffuse 6/sec. rhythm of moderate voltage.

From these findings it was concluded that the lesion was probably a mid-line one involving the visual cortices, though indirect pressure from below the tentorium was not ruled out. Clinically the case was regarded as a posterior fossa lesion, and accordingly this area was explored, but no abnormality was found. Three weeks later a ventriculogram showed a large filling defect in the posterior part of the 3rd ventricle. A right ventriculostomy was done and the 3rd ventricle explored,

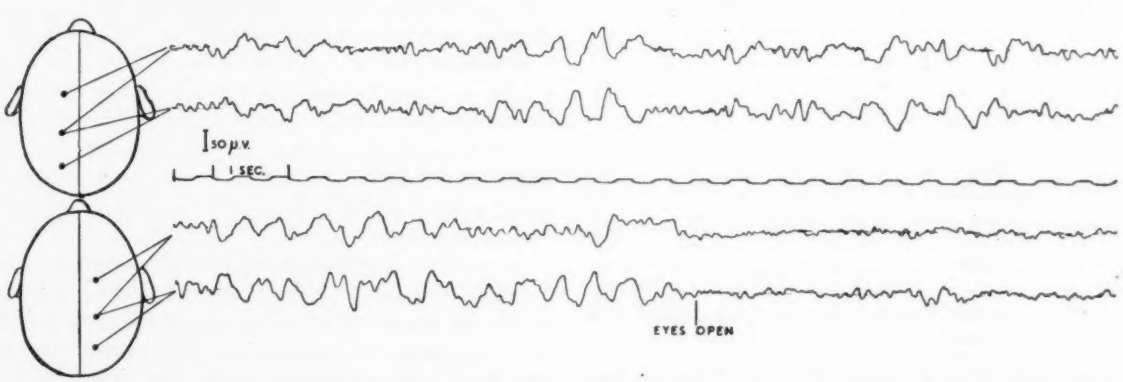

FIG. 2.—Case 1. Showing phase-reversal of 2/sec. waves in both parietal areas. On the right side the effect of eye opening is shown. There is also a well-defined 6/sec. rhythm.

revealing a fairly large spherical tumour arising from the region of the posterior commissure. A partial removal was attempted, but the patient died shortly after the operation. The tumour was an astrocytoma rising from the posterior commissure, with limited extension into surrounding structures.

In the type of record in which several frequencies are present it is usually the slowest which is of greatest significance, and phase-reversal of it correspondingly more so. Sometimes phase-reversal of two slow frequencies occurs in different positions, in which case that of the slower is usually of the greater significance, though one's conclusion may be modified by the presence of the faster; more will be said about this later, in connection with the 4–7/sec. frequency band.

There must, presumably, be a point or points, at which phase-reversal of any frequency occurs, but in many cases either the search for it is inadequate or it is inaccessible. In these circumstances reliance must be placed on finding the site of maximum intensity of the slow waves. It is difficult to define what is meant by "maximum intensity" as it involves a somewhat subjective assessment of amplitude, number, and possibly "slowness" of the abnormal waves: when it is considered that there may be a generalized background having very similar characteristics to those of the local disturbance it is apparent that this method may be by no means easy to apply; nevertheless very satisfactory localizations can be made by it, sometimes of surprisingly small extent.

Silent Areas.—Early in the history of the e.e.g. it was established (Foerster and Altenburger, 1935; Walter, 1936, 1937) that tumour tissue is electrically inert, and as a corollary, silent areas over superficial tumours have been described. In the present series they have only been convincingly demonstrated on two occasions; allowance should be made for the obvious difficulty of such a demonstration on two channels. In one, a small cyst was covered by about 1 in. of macroscopically normal tissue; in the other a large para-torcular meningioma corresponded with the silent area. In the first case, if not in both, it seems probable that what was found was an area of equipotential rather than a truly silent one.

Parasagittal Tumours.—It will be seen that 9, or 10·25 per cent. of the "accessible" tumours gave records which were not definitely abnormal. Two of them were basal tumours, and the remaining seven were all parasagittal, in part at least (the gliomata were, of course, of ill-defined extent). The difficulty of localizing parasagittal tumours has been noted (Gibbs and Gibbs, 1941), but such striking confirmation was unexpected, and is difficult to explain. It has been suggested that this difficulty is consistent with the routine practice of antero-posterior recording, and might be lessened by the use of transverse leads. This may perhaps be so, but does not account for the absence of definite abnormality. While it is possible that certain parts of the brain are incapable of producing delta waves, perhaps through lack of a pace-making mechanism, it is hardly plausible to suppose the entire para-sagittal cortex to be in such marked distinction from the adjacent cortex with which its several areas are cytologically and functionally allied. While rejecting these two possible explanations it must be confessed that no better alternative is offered.

Three of the above seven tumours were meningiomata; this rather high proportion is in keeping with the general observation that on the whole they cause less electrical disturbance than malignant tumours, or, in slightly different form: the degree of disturbance is proportional to the rate of growth. There are very marked exceptions to this rule, but it is a fairly satisfactory approximation.

Hyperventilation.—This was done in a number of the cases, but was impossible or inadvisable in the remainder. The usual procedure was to overbreathe for three minutes, recording for the last half-minute, and a period after the return to normal breathing depending upon the observed result. As a rule it was impracticable to pay much attention to the patient's blood-sugar level which, for routine purposes, implies the avoidance of recording too soon after a meal.

Hyperventilation was performed in 43 cases in all. Of these, 29 showed substantially no change, and 11 some increase either in irregularity or amplitude, or both, often with some general tendency to slowing. The remaining 3 gave more definite abnormal responses. In one a period of gross slow activity was terminated by a syncopal attack and was almost certainly circulatory in origin. The other two were both brain-stem gliomata; one showed a prolonged bilateral 2½–3/sec. response, and the other a unilateral 5/sec. discharge; there was nothing in the clinical state of the latter to explain the unilaterality, and the resting record was normal.

In general it can be said that the commonest result of hyperventilation in tumour cases is a tendency towards accentuation of those abnormal features already present, and that little, if any, assistance is to be expected from it.

Theta Rhythm.—Discussion of the group of midline and basal tumours has been postponed to this point because a new conception of some importance is involved. Among the tumours of this group are eight of the pituitary or suprasellar region and one epidermoid of the middle fossa, eroding the body of the sphenoid; that is to say: nine tumours lying in and around the pituitary fossa and involving, to great or less extent, the nervous structures in immediate apposition to it. With one exception (a pituitary tumour present for at least 34 years) these cases all showed a more or less well-marked pre-central or central rhythm within the range of 4–7/sec. Grey Walter, in a verbal communication to the E.E.G. Society, April, 1943, suggested that there might be some special association between the 4–7/sec. frequency band and tumours of the basal ganglia; he has recently (E.E.G. Society Meeting, February, 1944) reaffirmed this belief on the basis of thirty cases, confirmed at operation or post

mortem, and proposes that the letter ⊖ should signify this rhythm.

The present material amply supports these views. In the eight cases mentioned above the rhythm has always been bilateral, though not necessarily symmetrical, and in some was associated with other rhythms; in such cases the tumours were found to have their greatest projection towards the side on which the Theta rhythm was most marked.

Case 2.—P. H., male, age 38. This patient had a 10 years' history of headaches, at first severe and associated with vomiting, but later ameliorating. For 4–5 years his memory and mental capacity had deteriorated, and for the last two years he had been impotent. More recently he had experienced urgency of micturition and sometimes incontinence of urine. He was a pale thin man with soft waxy skin and scanty hair of female distribution. Cerebration was slow and somewhat inaccurate. There was bilateral optic atrophy and a bitemporal hemianopia. Apart from these eye-signs, there was some rather indefinite weakness of arms and legs, and spasticity of the left leg.

E.E.G. (Fig. 3).—Alpha rhythm: 12/sec., at about 25 micro volts, but very little could be distinguished.

The main component of the record was a bilateral 5–6/sec. rhythm, almost continuous, of fair regularity, at up to 90 micro volts.

It was not inhibited by eye opening, and was maximal in the pre-central regions.

Operation.—A right trans-ventricular approach revealed a rather large but otherwise normal lateral ventricle, with a patent foramen of Munro. A supra-sellar cyst of moderate size was bulging into its floor, but chiefly passing back under the anterior end of the 3rd ventricle. This was drained and its wall removed as far as possible. It appeared to have been roughly spherical and symmetrically placed about the mid-line.

Case 3.—J. F., female, age 22, had a history of 6 years secondary amenorrhœa, 6 months frontal headaches, and 5 months blurring of vision of the left eye and occasional diplopia. Appetite had recently increased and she had gained a stone in weight in a month. She had also been drinking more lately, with attendant polyurea.

When examined she had V.A.R. 6/18. V.A.L. 6/12: and bitemporal visual field defects, chiefly of the upper quadrants. The tone of the left leg was rather greater than that of the right and on the left side she had an equivocal plantar response. The c.s.f. was under a pressure of 200 mm. of c.s.f. and contained 70 mgm./100 c.c. of protein.

E.E.G. (Fig. 4 (1)).—Alpha Rhythm: 16/sec., regular, at about 20 micro volts. In all positions there was an almost continuous, rather irregular 5–7/sec. rhythm, mostly of fairly low voltage, but up to 50 micro volts. Hyperventilation produced little change.

Operation.—A suprasellar tumour was found, partly cystic, but largely solid. As much as possible was removed and the patient ultimately discharged to another hospital for deep X-ray therapy.

She returned 2½ months later because of an exacerbation of her headaches. The chief changes noted at this time were: V.A.R. 6/60. V.A.L. 6/18, hypertonus of left arm and leg, with some weakness of dorsiflexion of the left foot and a plantar response on the left side which was definitely extensor.

E.E.G. (Fig. 4 (2) and (3)) showed a bilateral 5/sec. rhythm, at up to 100 micro volts, maximal in the pre-central regions, where phase reversal was present on the right side. In the right frontal area there was a gross irregular discharge from 1/sec. to 3/sec., at up to 150 micro volts, which showed phase-reversal over the frontal pole.

The patient died three weeks after readmission, and the post mortem revealed a tri-lobed cystic tumour, one lobe of which occupied the enlarged pituitary fossa, while one projected forwards and somewhat to the left;

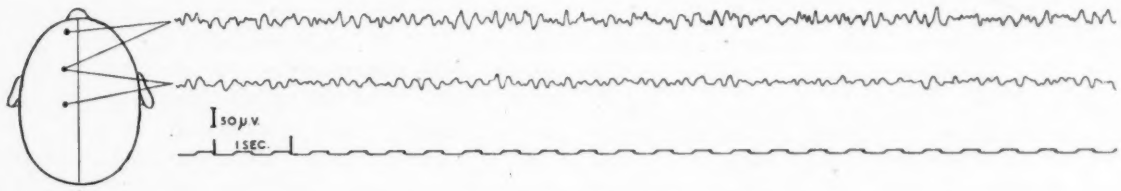

FIG. 3.—Case 2. Showing frontal 5–6/sec. rhythm.

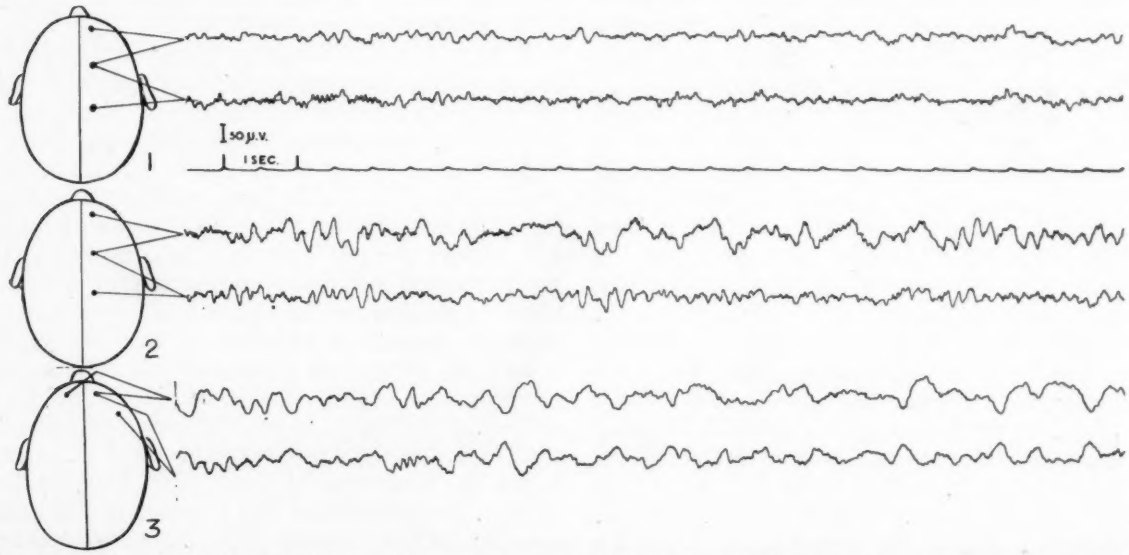

FIG. 4.—Case 3. (1) Showing 16/sec. Alpha-rhythm and 5–7/sec. frontal Theta rhythm. (2) The same position 4 months later showing increased amplitude of 5/sec. rhythm, and also frontal Delta activity. (3) Same date as (2): phase reversal of Delta rhythm over Right frontal pole.

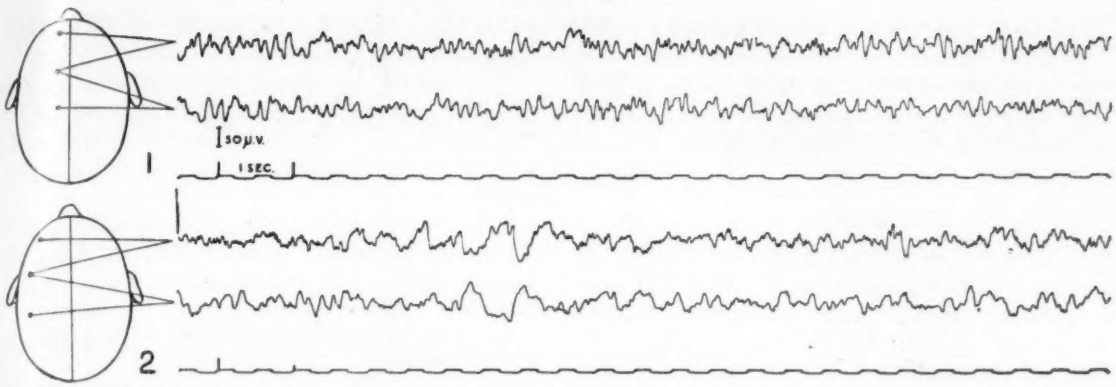

FIG. 5.—Case 4. (1) 6–7/sec. rhythm in left frontal region. (2) Phase-reversal of Delta rhythm in left fronto-temporal region.

the largest lobe, 5 cm. in diameter, projected forwards, upwards and to the right into the right frontal lobe.

Case No. 3 is of particular interest as it illustrates a parallelism between changes in the clinical state, anatomical findings, and the e.e.g. It is also a good example of the asymmetrical Theta rhythm, in this case associated with focal delta activity, and suggests the wider application to which the concept of the Theta rhythm can be placed, as exemplified by the following:

Case 4.—L. C., male, age 39, had a 10-year history of petit mal attacks, which, after six years, began to be interspersed with generalized convulsions, without aura or localizing features, at the rate of 1–2 a week. Three months before admission he began to have attacks of occipital headache, with dizziness, usually occurring on looking up from his work and relieved by returning his head to its original position. In time the headache became a more constant dull frontal ache, and was associated with nausea and vomiting. The chief physical signs were a fairly severe mixed aphasia, mild papillœdema and a right inferior homonymous field defect. There was a mild right hemiparesis, most marked in the face and arm.

E.E.G. (Fig. 5) showed an almost continuous 6–7/sec. rhythm at about 50 micro volts, with phase-reversal in both pre-central para-sagittal positions. There was also an irregular slower discharge of rather higher voltage, maximal on the left side, where phase-reversal occurred in the fronto-temporal region. This was reported as being probably due to a left fronto-temporal basal lesion.

On the evidence of a ventriculogram the tumour was thought to be in the left temporal region, and accordingly this area was explored, rather far back. An area of what appeared to be gliomatous cortex was exposed, but on incising this a firm globular tumour was revealed. This proved to be a meningioma, weighing 46 grams, arising from the dura of the petro-sphenoid ridge, towards its medial end. The tumour was removed, apparently intact, but unfortunately the patient died some months later from an extremely rapidly growing recurrence.

Several cases similar to the above have been seen, and there is every reason to think that the Theta rhythm concept is a useful addition to the accepted methods of tumour localization, but the exact origin and physiological significance of the rhythm are still in doubt. Although the causal lesion is almost certainly basal this does not necessarily imply that one is recording basal potential changes; it is possible that a basal pace-maker is activated by the lesion, and that the potential changes recorded are of cortical origin, though under the influence of this pace-maker. Jasper (1941) has claimed to have recorded basal potentials by means of a sphenoidal electrode, but as this was the middle electrode of three, the other two being symmetrically placed over the frontal cortex, there is no reason why the recorded potential changes should not have occurred at the cortex, provided a common pace-maker is postulated. It is at least probable that the whole e.e.g. is of cortical origin, though under the influence of deeper structures.

The Theta rhythm occurs, of course, in conditions other than basal tumours and is particularly well seen as a component of the very mixed records associated with hydrocephalus of the 3rd ventricle, and tumours in the ventricle, as exemplified by Case 1. In such records the distribution of the rhythm is usually more posterior than in those of the hypothalamic region, or it may be generalized. It is also fairly frequently seen following concussive head injuries, and Silverman (1943) and Hill (1944) have described bilaterally synchronous 4–7/sec. rhythms associated with aggressive psychopathy, though they respectively locate these as pre-frontal and post-central. These observations are not incompatible with lesions of the hypothalamus (Hill, 1944), and the evidence from the tumour cases points to the hypothalamus and thalamus as the source of the rhythm.

In a few instances a well-defined unilateral 4–7/sec. rhythm has been seen in association with a superficial cerebral tumour. I have regarded this as a "tumour" phenomenon, rather faster than the usual range, but Walter (personal communication) has pointed out that it could be explained by the cutting off of the cortex from thalamic control by the deeper parts of the tumour. This may well be so, but I think it would be a mistake at present to give to certain frequencies values which are too absolute—the most familiar normal rhythm is 10/sec.±about 20 per cent., but 10/sec. rhythms are not necessarily all normal; nor does the alpha rhythm, slowed by trauma to perhaps 7/sec., necessarily differ in character from the normal except in its frequency.

Many tumour records contain waves lying in the

4–7/sec. range, but not as a clearly defined rhythm; it is possible that they are of the same origin, but, for the utilitarian purpose of localization, a fairly definite rhythm is necessary before one is justified in giving to it the special Theta significance.

Conclusion

The usefulness of the e.e.g. in tumour localization is beyond doubt, and it has an occasional value as a pointer in tumour differentiation. It is not proposed to compare the respective merits of the various methods of localization because all methods available and suitable should be applied, and regarded as complimentary, but it should be noted that the e.e.g. has one very great advantage over air-replacement methods: it is entirely free of discomfort or danger to the patient. Positive findings in the e.e.g. are probably about as reliable as in either ventriculography or clinical methods, but, as in them, anomalous localizations do occur, sometimes explicable after the event and sometimes not.

The tumours which lend themselves most readily to localization are those of the free convexity which are rapidly growing, but even among these there are some which show only a little diffuse abnormality. From the present series it is possible to choose several pairs with very similar lesions, one of which was easily localized by gross slow activity while the other showed a minimal general change. It may well be that investigation of such negative results will prove as profitable in the elucidation of cerebral behaviour as that of the more spectacular dysrhythmias.

Summary

Results obtained by e.e.g. in 120 intracranial tumours and 5 abscesses are tabulated and discussed. About 50 per cent. of accessible lesions were correctly localized. It is not considered that cerebellar tumours are normally localizable.

There is a somewhat greater tendency to slowing of the alpha rhythm than in other cases, including acute head injuries. Asymmetry of alpha rhythm is an inconstant but sometimes useful finding.

The record associated with raised intracranial pressure is exceedingly variable, and bears no direct relationship to the height of the pressure nor to the degree of papillœdema, but some to the state of consciousness.

The " ideal " method of localization is the finding of phase-reversal of slow waves, but not infrequently one must depend upon their maximum intensity. Where a number of slow rhythms are present the slowest is usually of major significance for localization.

From the accessible tumours nine normal records were obtained, of which seven were from parasagittal lesions, emphasizing the well-known difficulty in their localization.

Hyperventilation is unlikely to do more than accentuate the features of the resting record.

It is suggested that the 4–7/sec. frequency band or Theta rhythm has a special significance, and is associated with lesions in the region of the third ventricle. A number of cases are described in which this concept has proved of localizing value.

My thanks are due to Mr. Harvey Jackson, whose cases provide the material for this paper, and to E. B. C. Hughes and W. Grey Walter for their advice and criticism. Three of the cases cited were referred to this Hospital by Dr. J. St. C. Elkington, Nos. 1 and 4 from the National Hospital, Queen Square, and No. 3 from St. Thomas's Hospital.

References

Foerster, O., and Altenburger, H. (1935). *Deutsch Z. Nervenheilk.* **135,** 277.

Gibbs, F. A., and Gibbs, E. L. (1941). *Atlas of Electroencephalography.* Boston.

Hill, J. D. N. (1944). *Proc. roy. Soc. Med.*, **37,** 317.

Jasper, H. H. (1941). See Penfield and Erickson, *Epilepsy & Cerebral Localization.* London.

Silverman, D. (1943). *Arch. Neurol. Psychiat (Chicago),* **50,** 18.

Smith, J. R., Walter, C. W. P., and Laidlaw, R. W. (1940). *Ibid.*, **43,** 472.

Walter, W. G. (1936). *Lancet* (ii), 305.

—— (1937). *Proc. roy. Soc. Med.*, **30,** 579.

Williams, D. (1939). *Brain*, **62,** 321.

THE ELECTROENCEPHALOGRAM IN TRAUMATIC EPILEPSY

BY

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(RECEIVED 17TH OCTOBER, 1944)

THE material used in earlier studies of the immediate and remote effects of injury upon the human e.e.g. (Williams, 1941 (a) and (b)) gave little information upon the relationship of these effects to the development of traumatic epilepsy. In the three years which have since elapsed much more data have been accumulated on traumatic epilepsy, and more definite conclusions than were possible at that time can be made on this aspect of the subject. Other papers upon the general and focal changes in the e.e.g. associated with trauma have been published (Jasper, Kershman and Elvidge (1940) and Heppenstall and Hill (1943), and Jasper and Penfield (1943) have described changes associated with traumatic epilepsy. Reporting upon 81 patients studied by the e.e.g., of whom 32 had had a cerebral operation, they described focal abnormality in 90 per cent., with a generalized disturbance in the remainder. The most characteristic change in the e.e.g. in these cases was the presence of high-voltage spikes, although slower waves were also seen, and the authors commented upon the close association of the position of the observed cerebral lesion in the 32 operated cases, and the site of focal discharge in the e.e.g. They thought that the 10 per cent. of patients who did not show such a focus may have been suffering from essential, rather than traumatic, epilepsy. The importance of trauma in causing focal changes in the e.e.g. has also been established by Gibbs, Merritt and Gibbs (1943).

The present enquiry is not so much concerned with the focal nature of the changes in the e.e.g. in traumatic epilepsy as with the relationship of different abnormalities in the e.e.g. of patients with head injuries to the subsequent onset of traumatic epilepsy. Evidence based on the observation of a large number of subjects will be presented, and this evidence will be related to the possibility of predicting the onset of traumatic epilepsy by means of electroencephalographic examination.

Method

Material. There were in all 1,002 subjects who were divided upon clinical evidence into the following groups:

(1) 241 normal, healthy controls with no personal history of head injury, faints or fits;
(2) 234 patients with head injuries without epilepsy;
(3) 210 patients with traumatic epilepsy;
(4) 275 patients with apparently idiopathic epilepsy;
(5) 42 patients who were examined by the e.e.g. before and after the onset of traumatic epilepsy.

The subjects were all adults serving in the armed Forces, those with head injuries or epilepsy being hospital patients who were examined by electroencephalography during routine investigation. The normal controls were also service personnel of the same group, mainly derived from the staff of the hospital. An account of these normal subjects has already been given (Williams, 1944). The patients with head injuries were selected from several thousand examined during three years, but they were only specially selected in so far as those in whom there was doubt as to the presence of attacks, or as to the nature of the attacks, were rejected from the series. They were all patients in whom the severity of the injury or the persistence of symptoms had led to admission to a service hospital. They included patients with open and closed cranial injuries, and they were all investigated more than 4 weeks after the injury. The clinical and e.e.g. records of a sufficiently large number of consecutive cases were scrutinized to give adequate samples for statistical comparison, but the relative numbers do not reflect the actual incidence of epilepsy in the total series. These head injury patients, both with and without fits, were divided into those with closed and penetrating injuries. The last group of patients, by their nature few in number, was followed up specially. These were patients who had had a head injury, had been fully investigated, and who had at a later date developed fits which led to their re-investigation. Particular importance was attached to the results in these patients.

All the groups were taken from the same restricted population of service men; the patients with traumatic epilepsy had been drawn from the same population of head injury patients as those without fits, and the last small group of traumatic epileptics only differed in that the patients had been examined before and after the onset of epilepsy. The groups may therefore be compared with each other with impunity.

Technique. The technique of recording, and the method of examination and of assessing the e.e.g. records, with a description of the different types of abnormality, has already been given in detail (Williams, 1941 (a) and 1944). In brief, records of at least 15 minutes duration were obtained from a three- or six-channel Grass ink-writing electroencephalograph, two rows of saline pad electrodes being placed over each hemisphere. The electrodes were, as a routine, connected in pairs to give "bipolar" recording; some records were checked with simultaneous "monopolar" recording. The records were divided into normal and abnormal without knowledge of the clinical history of the patients, upon the basis of a norm which excludes 12 per cent. of the apparently normal group. The records classified abnormal were divided into three groups —those with characteristic epileptic outbursts (larval outbursts), those with other less well-defined paroxysmal disturbances, and those which although classified abnormal did not contain any episodic abnormal activity. Examples of these different types of abnormal e.e.gs. recorded in epileptic subjects have already been published (Williams, 1944, Williams and Sweet, 1944).

Having done this, features in the clinical story were related to the type of e.e.g. change which had been

found. In most instances the subject was only investigated once, but in the group of patients in whom e.e.g. records had been obtained before the first fit, other records were obtained when possible at varying intervals of time after it.

Results

The distribution of normal and abnormal e.e.g's. in the five groups already described is shown in Table I. The percentages are corrected to the nearest whole figure.

TABLE I

Features in the e.e.g.	Percentage of subjects				
	1 Normal (241)	2 Head injury without fits (234)	3 Head injury with fits (210)	4 Recorded before traumatic epilepsy began (42)	5 Idiopathic epilepsy (275)
Larval epileptic outbursts	0	0	8·6	5	27
Other paroxysmal outbursts ..	0·8	14	17	18	29
Other forms of abnormality ..	11	46	37	38	19
Total abnormal ..	12	70	63	60	75
Normal ..	88	40	37	40	25

It will be seen in Table I that the proportion of subjects with different types of e.e.g. is about the same in the small group of head injury patients who were investigated before their first fit (column 4) as in those investigated after fits had commenced. (column 3). As the only difference between these two groups lies in the time of recording the e.e.g. they will for the moment be considered together as traumatic epileptics. The group of 42 patients with e.e.g's. before the first fit will be discussed in more detail later.

The distribution of the different forms of abnormality in the five groups of subjects is shown as a histogram in Fig. I. The following observations may be made upon the figures presented.

LARVAL EPILEPTIC OUTBURSTS are not found at all in two large groups of subjects who have not had epileptic fits. This is so whether or not a head injury has been sustained. On the other hand, 9 per cent. of traumatic epileptics and 27 per cent. of idiopathic epileptics show these outbursts. These differences are reliable statistically. It has been stated elsewhere (Williams, 1944) that larval epileptic outbursts are very rarely seen without overt fits, and that their presence indicates an established epileptic state. From columns 3 and 4 in Table I it is clear that the 2 patients out of the 252 (5 per cent. of 42 in column 4) with a head injury who showed larval outbursts in the e.e.g. in the absence of fits, developed fits shortly afterwards. This indicates that the presence of these outbursts in a patient's e.e.g. record makes the likelihood of traumatic epilepsy very great indeed. Columns 3, 4 and 5 show that the chance of observing a larval epileptic outburst in the e.e.g. of idiopathic epileptics is three times as great as in traumatic epileptics.

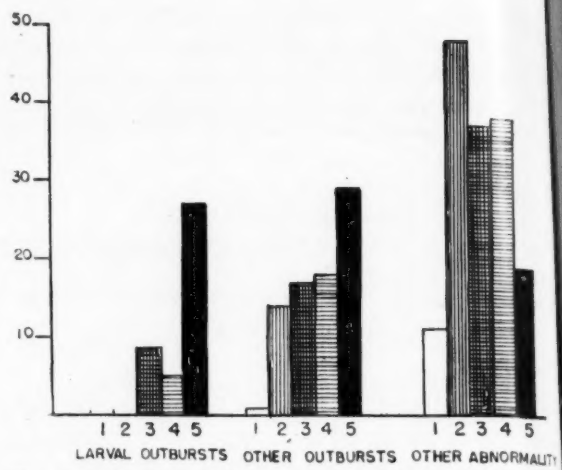

FIG. 1.—The figures 1 to 5 on the abscissa refer to the numbered columns in Table I, viz., 1, normals; 2, head injuries; 3, traumatic epileptics; 4, records made before the onset of traumatic epilepsy; 5, idiopathic epileptics; the ordinate represents the percentage of each group of cases.

OTHER PAROXYSMAL OUTBURSTS in the e.e.g. are distributed in the five columns in Table I in the same general manner as the larval outbursts, but the differences between the columns are not so distinct. Although these outbursts are uncommon in normal subjects, they are nearly as frequently seen in the group of head injury patients who have not developed fits as in those who have. It is certain, of course, that some of the first group will develop fits at a later date since the time of recording the e.e.g. after the injury was sometimes as short as a month, and was in most cases under a year. Nevertheless, it seems that the presence of paroxysmal outbursts in the post traumatic e.e.g. does not necessarily indicate the development of traumatic epilepsy, although it has been shown that in other pathological conditions these outbursts usually indicate an epileptic tendency (Williams, 1944). This statement is probably also true for head injuries, for it is likely that sometimes a liability to traumatic epilepsy which is reflected in the e.e.g., may not become overt in the form of fits for many years. In an earlier paper (Williams, 1941 (a)) it was shown that reversible changes in the e.e.g. recorded shortly after severe brain injury were indistinguishable from those seen in epileptics, and it seemed as though trauma gave rise to transient cerebral changes conducive to epilepsy which were reflected in the e.e.g. of many more subjects than developed traumatic epilepsy later. The clinical evidence of these changes is the early occurrence after a head injury of fits, which have no relationship to the later onset of traumatic epilepsy. It follows that in some traumatic epileptics other factors than the injury must be required to potentiate the latent epileptic liability. The development of these factors may

account for the great delay in the onset of fits in some cases of head injury. This line of enquiry might well prove fruitful, but the results so far presented in Table I merely indicate that if these outbursts in the e.e.g., which are usually associated with epilepsy, occur more than a month after a head injury they are only associated with overt fits in a little more than half the cases. Conversely these changes occur in a sixth of the patients who develop traumatic epilepsy, compared with nearly a third of idiopathic epileptics.

Taking all the transient disturbances in the e.e.g. together it is seen that they occur in less than 1 per cent. of normals, in 14 per cent. of uncomplicated head injuries, 25 per cent. of traumatic epileptics and nearly 60 per cent. of idiopathic epileptics. Further information upon the relationship of these disturbances to the later onset of traumatic epilepsy can be obtained by determining the incidence of traumatic epilepsy in groups of patients with and without transient disturbances in the e.e.g. The results of such an enquiry in the present series of head injury cases are shown in Table II.

TABLE II

Head injury	E.E.G. transient outbursts	Number of cases	Traumatic epileptics		χ^2
			Number	Per cent.	
Closed	0	178	8	4·5	8·5
	+	35	7	20·0	
Open..	0	75	6	8·0	3·8
	+	28	7	25·0	

The probability that the differences in Table II are due to chance is less than 1 in 100, and 1 in 20 respectively. The probability of both the differences between the groups with and without transient outbursts being due to chance is less than 1 in 100. Table II therefore shows that there is greater risk of epilepsy after a head injury, whether closed or penetrating, if transient outbursts of abnormal waves are seen in the patient's e.e.g. The likelihood is increased in these cases by about 4 times.

NON-SPECIFIC ABNORMALITY. The proportion of normal and epileptic subjects who are considered to have abnormal records has been discussed elsewhere (Williams, 1944) and has been investigated in detail by others, notably Jasper and Kersham (1941), Gibbs, Gibbs and Lennox (1943) and Finley and Dynes (1942). The total incidence of abnormality in the e.e.gs. of subjects with head injuries seems, from columns 2, 3 and 4 of Table I, to be unaffected by the presence of epilepsy. As the incidence of transient outbursts, and particularly of "larval" attacks, is greater in the epileptic group, it follows that abnormality of a non-specific kind alone is less commonly seen in them. The dysrhythmias of this indeterminate sort which are seen, are sometimes the result of the injury, and in others they represent evidence of pre-traumatic abnormality in the e.e.g. (Williams, 1941 (b); Heppenstall and Hill, 1943). Although groups of subjects with such abnormal e.e.gs. have been shown to contain a higher proportion of epileptics than is found in the population at large, the presence of this kind of abnormality in patients with head injury does not seem to be closely related to the likelihood of traumatic epilepsy. It must be borne in mind, however, that there is more likelihood of having both an abnormal e.e.g. and traumatic epilepsy after a severe head injury than after one of mild degree.

CLOSED V. PENETRATING INJURIES.—Table III shows that the incidence of paroxysmal outbursts of the kind usually associated with epilepsy are much more frequent in a group of patients with penetrating head injuries than in a similar group with closed head injuries. For this table $\chi 2$ is 18·4 and P is less than 0·01, indicating that the likelihood of the difference being due to chance is less than 1 in 100. The proportion with non-specific abnormality is by contrast about equal in the two groups. The incidence of traumatic epilepsy is higher when dural penetration has occurred (Ascroft, 1941), so that the relatively high incidence of "epileptic" changes in the e.e.g. in this series is explained. This high incidence without any change in other forms of abnormality might be expected from the results already presented.

TABLE III

Type of injury	Number of cases	E.E.G. findings (percentage of total cases)			
		Larval outbursts	Other transient outbursts	Other abnormalities	Normal
Penetrating	70	4	26	47	23
Closed ..	66	0	5	50	45

To summarize the observations made so far: an abnormal e.e.g. persisting after a head injury does not necessarily increase the likelihood of traumatic epilepsy, but the presence of episodic outbursts of abnormal waves does. If these disturbances are organized into patterns considered to be larval attacks, epilepsy is almost certain to supervene, while transient disturbances of a less dramatic kind add materially to the likelihood of its onset.

E.E.Gs. RECORDED BEFORE THE ONSET OF TRAUMATIC EPILEPSY.—In all the 42 cases in column 4 of Table I the patient had been investigated while under treatment in hospital for the effects of a head injury. While still in hospital, or more commonly on return to duty, one or more epileptic fits had occurred and the patient was referred back to hospital. It was thus possible to investigate each of these cases before

and after the onset of epileptic fits. The interval between the two investigations during which fits commenced ranged from 3 months to 3 years. The number of cases with different types of e.e.gs. recorded before the fits began is shown in column 4 of Table I, and, as already noted, is similar to the figures for e.e.gs. recorded after the onset of traumatic epilepsy

The changes observed between the records made before and after the fits began seemed to be unpredictable, but the numbers of cases with each kind of record were insufficiently large to have any comparative value alone. It was commonest for the e.e.g. to remain unchanged in any particular after the onset of traumatic epilepsy, whether it had previously been normal or abnormal, and whether or not it had contained episodic disturbances before the fits began. When changes occurred they were invariably caused by the appearance of episodic disturbances in a record which had previously been either normal or abnormal. Observation of these episodic disturbances in the e.e.g. record may have been to some extent governed by chance, and transient disturbances must have been missed because of the relatively brief period of recording which was dictated by the demands made upon the department. This would be particularly likely where the episodes were infrequent. Even so, disturbances of an epileptic type were seen in nearly a quarter of cases before fits began, and in some instances they preceded the first fit by more than a year.

Several samples of e.e.gs. recorded before and after the onset of symptomatic epilepsy have already been described at length (Williams, 1944). As the types of records seen in this series, and their relationship to the type of clinical fit, is the same as in those in the earlier report, further description is unnecessary.

Focal Abnormality.—A specially important point which has not been covered is the relationship of the position of origin of transient outbursts of an epileptic type to the focal abnormality seen in the e.e.g. of patients with penetrating wounds. Jasper and Penfield (1943) have stressed the frequent occurrence of foci of abnormal discharge in the e.e.g. of patients with traumatic epilepsy, and have shown the close relationship of the epileptic focus to a lesion which was demonstrated at operation in 30 out of 32 cases. Although the present investigation was not concerned primarily with the foci of discharge, such foci were found in a large proportion of cases of traumatic epilepsy, in contrast to the group of idiopathic epileptics. These findings coincide with those of Gibbs, Merritt and Gibbs (1943). Foci of non-specific activity are common after head injuries, and have been adequately described, Heppenstall and Hill (1943). When such abnormality existed in the present series in association with episodic "epileptic" activity, the sites of origin of the two kinds of discharge were often at or near the same point on the scalp. This focus was, however, in many cases merely a zone of maximal abnormal activity where fast waves ("spikes") could be picked up with greater facility than from elsewhere. Exploration of other points on the scalp showed that the discharge of spikes was widespread, with frequently another zone of increased abnormality on a symmetrical point on the other side of the scalp. Sometimes, however, the epileptic discharge would not coincide with the area of gross brain damage. For instant, bifrontal discharge might accompany an area of slow activity elsewhere (Case 2).

The relationship which the slow abnormal waves of cerebral damage bears to the episodes of faster, high voltage waves of epilepsy should be considered in time as well as in space. It might be expected that they would relate spatially, but a close temporal relationship cannot be found, while the possibility of abnormality of the episodic type having been present in the pre-traumatic e.e.g. further confuses the picture.

Immediately after a head injury it is usual to find gross abnormality characteristic of severe cerebral damage which during the period of resolution may mimic the picture of epilepsy, but which in a few weeks subsides with the gradual reappearance of normal rhythms (Williams, 1941 (a)). For this reason all the cases of head injury included in this series were examined more than four weeks after injury. At some point in this period of recovery the other kind of abnormality appears, but the time of its appearance is very variable and its relationship in time to the onset of traumatic epilepsy is also variable. Table I shows that episodic activity is less than half as common in traumatic epilepsy than in idiopathic, and it is certainly very difficult to observe any abnormality in the e.e.g. of some traumatic epileptics in spite of frequent recording between seizures. Therefore, it is likely that, in some instances, the first demonstrable sign of the development of the epileptic state will be an overt fit. Episodic changes appearing in the e.e.g. before the first fit are nevertheless common, and by serial recording over months the process has been closely observed. In these cases it is evident that months after the injury an abnormal state is established which steadily increases until it finds expression first in an indefinite dysrhythmia, later in short episodes of abnormality, later in larval epileptic outbursts of the more clearly defined sort, and finally in a frank epileptic fit.

This process is most easily seen in penetrating wounds, for the disturbance can be studied in the neighbourhood of the local injury. Case 1 is an excellent example of it.

Case 1.—A gunner, aged 21, sustained a penetrating wound of the right frontal lobe as a result of a bomb explosion on 9th April, 1941. He remembered the whistle of the bomb before he was struck, but had a retrograde and post traumatic amnesia of about a second. He remained perfectly alert afterwards.

Nine hours later he was fully examined in hospital. There was a large, jagged wound of the right frontal region with shattered bone and much brain tissue extruding through it. Full neurological examination failed to

show any disturbance of function. He was well-orientated and fully conscious. To special testing there was slight defect of recall and of judgment. X-ray showed that a large depressed fracture of the right frontal bone with many fragments driven into the right frontal lobe. A piece of bomb casing was lying just above the left supraorbital ridge, having probably traversed both the right and left frontal obes.

An e.e.g. recorded 10 hours after the injury was grossly abnormal. The report follows: " The e.e.g. was grossly abnormal. Electrodes were placed 2 inches in front of and 2 inches behind the scalp wound and in corresponding positions on the left side. From these positions rhythmic bursts of high voltage pure sine waves with a frequency of 2 a second were obtained. These outbursts were indistinguishable from subclinical epileptic outbursts that have been found in other cases of severe cerebral damage when a record is obtained within a few hours of the injury. When they occurred these outbursts were symmetrically distributed in the frontal poles but between them the record was more abnormal on the right side than on the left. Comparing the anterior and posterior electrodes it was evident that this abnormality was present in the frontal poles but not behind the wound. A sterile stainless steel electrode placed in the wound showed a focus of discharge from the area under the bone defect." Samples of the records are shown in Figs. 2 and 3. Toilet of the wound was carried out by Lt.-Col. E. H. Botterell, R.C.A.M.C. The scalp wound was excised, the bone defect enlarged, and all loose bone fragments removed. Ventricular fluid welled into the brain defect which was 2½ inches deep. After a clean field surrounded by apparently healthy brain was obtained the wound was dusted with sulphanilamide and completely closed. The projectile was left *in situ*.

Progress. The patient was a little drowsy but was fairly well-orientated during the next three days, and apart from a bifrontal headache he had no complaints. There were at no time any signs of disturbance of motor or sensory function. Daily lumbar puncture produced blood-stained fluid under a pressure of 300 mm. of cerebro-spinal fluid.

An e.e.g. on the third day showed no substantial change.

Four days after the injury a mild right facial palsy of upper neurone type was noticed and the patient was restless. He had been incontinent of urine three times.

A week later the wound had healed by first intention, the cerebro-spinal fluid was straw coloured, and there were no neurological signs. Psychometric testing showed that he was alert, fairly well-orientated and had normal powers of recall. His reasoning, judgment and arithmetical ability were slightly defective and he was thought to be too apathetic and passive.

Two weeks after the injury he was up and about the ward, symptom and sign free, but still showing evidence of defect of reasoning, calculation and judgment. He had been incontinent nine times since the injury, saying characteristically that he " could not be bothered to ask for a bottle." He was quite contented to be in a wet bed.

An e.e.g. 14 days after injury was reported upon as follows: " Records taken from both frontal lobes still show very considerable abnormality consisting of high-voltage 1 to 3 a second waves. This is much worse on the right side than on the left and a very beautiful phase reversal occurs when an electrode is placed a little to the right of the midline. This indicates that a focus of discharge of abnormal electrical activity is starting in this region. The episodes of high-voltage sine waves resembling epileptic outbursts have now disappeared " (Fig. 3).

Three weeks after the injury an air-encephalogram showed that the body of the right lateral ventricle was being pulled out toward the bone defect.

Five weeks after injury surgical repair of the bone defect was successfully undertaken. The dura was found to have regenerated considerably, and the area of exposed brain was only the size of a shilling.

Nine weeks after the injury detailed psychiatric testing failed to show any abnormality.

An e.e.e. recorded at this time was " well within normal limits throughout the hemispheres except for a small area in the right frontal lobe below the wound of entry. The abnormality in this area is slight and very well circumscribed " (Fig. 2 and 3).

Fourteen weeks after the injury he returned to duty. Twenty- two weeks after injury he had a tonic-clonic fit with tongue biting and incontinence. He had one more in the next year, and then 4 while asleep in the same day in rapid succession. All of the attacks were witnessed and more were focal.

Two years after injury he was re-examined in hospital

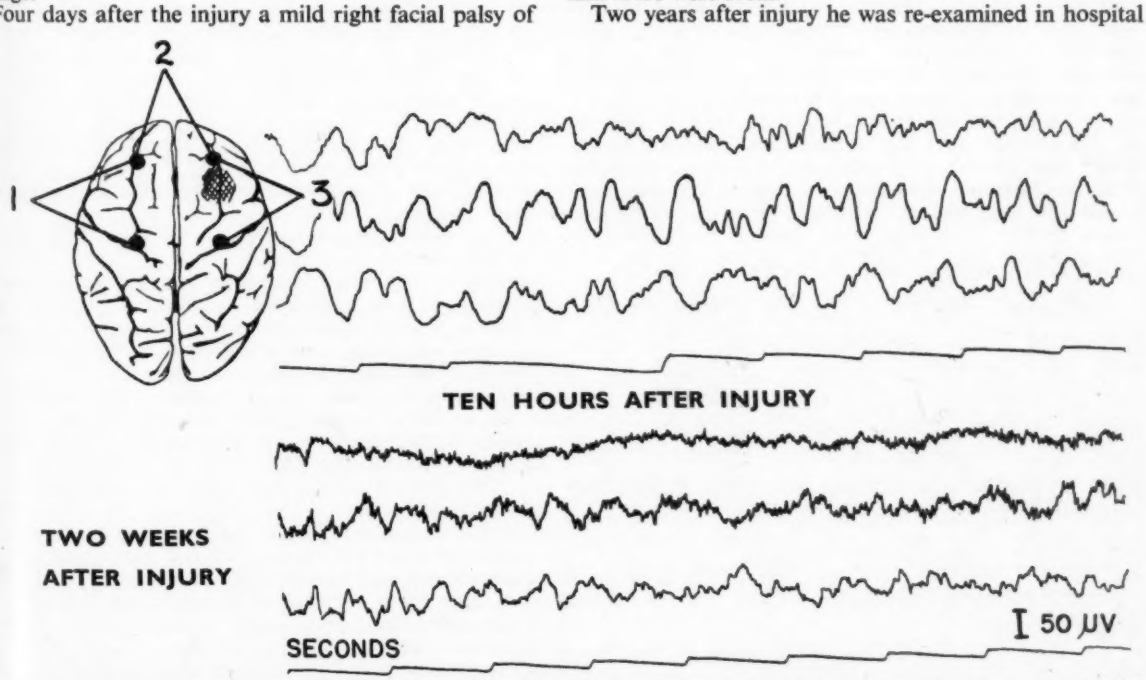

FIG. 2.—e.e.g. records from Case 1. The electrode placements are shown in the diagram, where the shaded area represents the position of surface injury to the brain. Contemporary descriptions of the records from which the samples in this and other figures have been taken appear in the case reports. The figure shows the subsidence with time of high voltage slow waves, the phase reversal in the lower two tracings indicating that the waves are emanating from the area of brain damage.

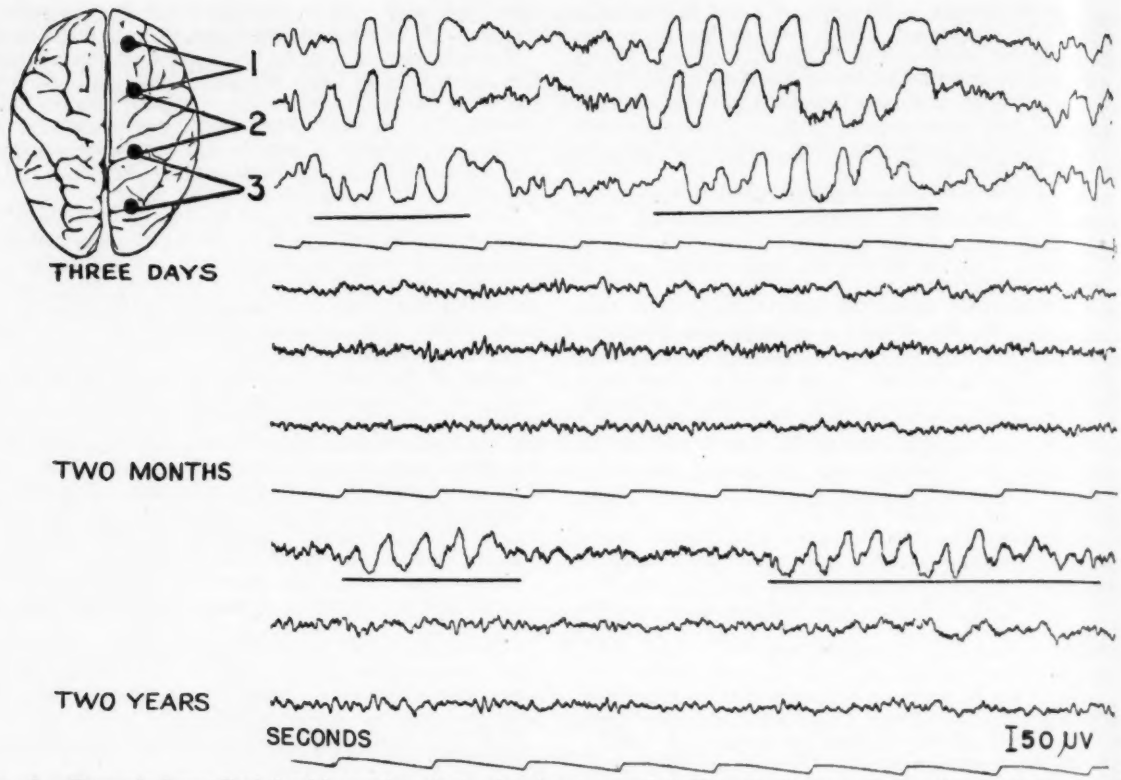

FIG. 3.—Records from Case 1 with routine electrode placements (cf. Fig. 2), 3 days, 2 months, and 2 years after injury, chosen to show the initial improvement and subsequent deterioration in the e.e.g. High-voltage slow waves, indistinguishable from those of epilepsy, are evident in all leads 3 days after the injury. These disappear with clinical recovery, and after two months the physiological dominant frequency is beginning to return. At this time low voltage 3 a second waves are limited to the frontal lobe. After 2 years bursts of high voltage 3 a second waves, of an epileptic kind, are obtained from the neighbourhood of the injury.

and there were no abnormal signs in the central nervous system. Psychiatric examination failed to show any defect in intellect or deterioration in personality. The cerebro-spinal fluid was normal in all respects, and the ventricular outline had not changed appreciably since the previous encephalogram taken 2 years before. The personal and family history revealed nothing of note—there was no evidence of epilepsy or migraine.

An e.e.g. at this time (11.3.43) showed " outbursts of high-voltage rhythmic slow waves of 2 to 4 a second which were considerably increased by overbreathing, but which were confined to the right frontal lobe especially under the bone defect. Records from positions elsewhere on the scalp were considered normal " (Fig. 3). The outbursts were thought to be epileptic in type.

COMMENT.—This is an example of severe laceration of the frontal lobes which healed by first intention after operation. Grand mal fits began 5 months after injury. The e.e.g. immediately after injury showed severe focal abnormality with generalized outbursts of waves indistinguishable from those seen in epilepsy. This abnormality subsided and except for slight focal abnormality of a non-specific kind the e.e.g. returned to normal. Subsequent records showed the development of typically epileptic discharges in the region of the original injury.

The focal epileptic disturbance, such as that seen in Case 1, may become widespread throughout the hemispheres, and when this has happened, even if a focus of discharge is evident, removal of that focus and of the damaged brain does not necessarily interrupt the epileptic process. This fact is shown in Case 2.

Case 2.—A signalman, aged 34, was struck in the right posterior parietal region by a piece of mortar bomb on 20th November, 1942. This entered the skull and passed through the brain to come to rest against the falx just anterior to the corpus callosum. It was subsequently shown that the site of entry was in the region of the angular gyrus on the right side. There was no amnesia and the patient walked back for treatment. He complained of diplopia and slight impairment of vision at that time. Rough examination shortly after the injury showed reduction of the left half of the visual fields without any other abnormal signs in the central nervous system.

Two weeks after injury he had slight bilateral papillœdema with hæmorrhage.

Four weeks after injury he reached an evacuation hospital where depressed fragments of bone were elevated and superficial necrotic brain was removed under local anæsthesia. Neither the foreign body nor the indriven bone fragments were touched.

Eight weeks after injury bilateral papillœdema was still present with hæmorrhage in the left retina. External ocular movements were full and except for some enlargement of the blindspots the visual fields were full.

Sixteen weeks after injury he was admitted to the Military Hospital for Head Injuries. He had a simple defect of accommodation-convergence but no other abnormal signs were found on full examination of the nervous system. Intellectually he was normal, and there was no evident personality disorder. In particular the optic discs and visual fields were normal. Lumbar puncture showed no abnormality. X-ray showed a circular bone defect in the right posterior parietal region, 1·5 cm. in diameter, with two small fragments of bone deep into it and a small metallic body in the midline just behind the sella.

An e.e.g. 4 months after injury (12.3.43). The report reads: " Bursts of abnormally fast waves with a frequency of 20 cycles were seen in the anterior parts of the hemispheres. They were more evident on the right

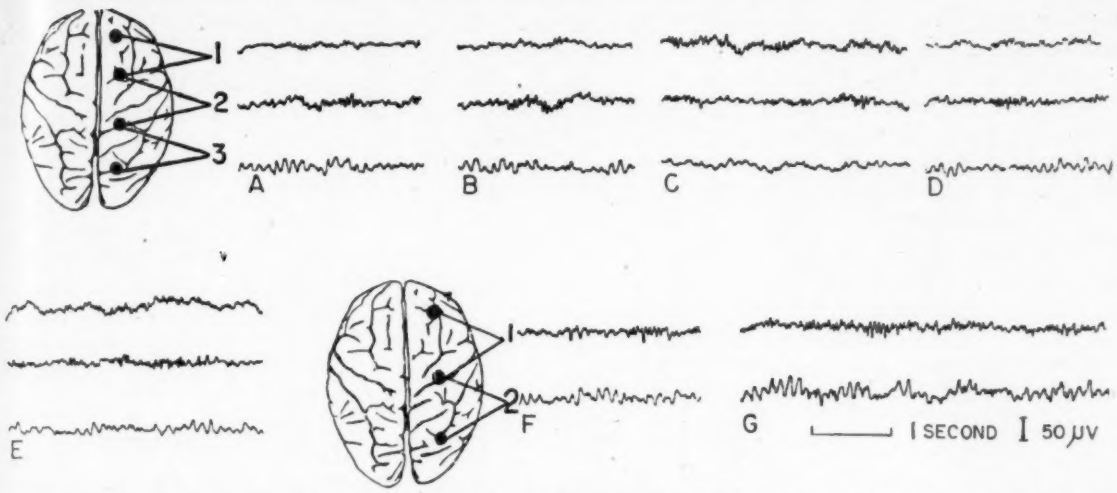

FIG. 4.—Samples of records obtained at different times from Case 2. The times of recording were as follows: A, 4 months after injury and 4 months before the first fit; B, 8 months after injury and 2 days after the first fit; C and D, immediately before and 10 days after removal of the cerebral cicatrix; E, F, and G, 4, 5, and 6 weeks after the operation. All samples show outbursts of fairly high voltage abnormally fast waves, lasting for 1 to 2 seconds and confined to the anterior part of the hemisphere. They were thought to represent epileptic outbursts, and were symmetrically distributed. They were not affected by removal of the scarred brain. Paper speed and amplification are constant.

side, where their maximum voltage was 30 microvolts. There were persistent abnormal waves with a sine form and with frequencies varying from 0·5 to 4 a second underlying a stable dominant frequency of 10 cycles in the neighbourhood of the scalp wound. These represented local cerebral damage of moderate severity. The frontal outburst of fast waves represented epileptic activity" (Fig. 4*a*). With orthoptic exercises the convergence-accommodation defect cleared up. As the wound was well healed and the patient was symptom and sign free it was decided not to explore the bone defect or to remove the indriven fragments. As he had had no fits he was discharged to duty.

Seven months after injury (6.7.43) he had a generalized tonic-clonic fit, witnessed by his wife. In it the head and eyes were turned to the side of the injury, but there were no other localizing features to be seen. He was readmitted to hospital (8.7.43).

An e.e.g. was recorded 2 days after the fit (8.7.43). The report was as follows: "The generalized episodic fast activity, thought to be epileptic in nature four months ago, is still present and is more evident. The focal disturbance consisting of slow sine waves has also persisted and is unchanged" (Fig. 4*b*).

Another series of records were made just before operation (23.7.43). The report read: "Careful exploration of the right hemisphere before operation showed that the abnormal slow waves of cerebral damage were strictly confined to the region of the bone defect. Phase reversals could be obtained for all these abnormal waves when an electrode was placed over the defect. The edge of the area of abnormal discharge was sharply defined, and the abnormal waves were being propagated radially from the site of the injury. There was no relationship between the site of injury and the position of the maximal epileptic discharges except that these discharges had a higher voltage on the affected side" (Fig. 4*c*).

Three weeks after the fit (26.7.43) the scar and indriven bone fragments were removed. At operation (Major C. A. Calvert) a right lateral bone flap was turned with the penetrating wound in its centre. The dura, which was adherent to the brain around the wound, was reflected and a large central scar was found. The arachnoid was very vascular in this region and there were dense vascular adhesions between arachnoid and cortex over the scar while a large cortical artery was firmly adherent to it. Beneath this there was a circular yellow gelatinous cortical scar 2·5 cm. in diameter. This scar was depressed almost 0·5 cm. below the surface o the surrounding normal brain. It was quite inactive to stimulation with a thyratron stimulator. The surrounding cortex, thought to be in the region of the supra marginal and angular gyri, was also inactive. The cortex was incised around the scar which was then completely excised. The scarred brain was cone shaped, the base of the cone extending to the trigone of the right lateral ventricle which was opened during the excision. Cerebro-spinal fluid welled freely into the wound and the opening was seen to be about 0·7 cm. in diameter. A clean, dry field was obtained and the wound closed in the ordinary way. There was no disturbance of sensory, motor or visual functions immediately after operation, and recovery was uninterrupted.

An e.e.g. which was recorded 10 days after operation (6.8.43) showed: "The episodes of epileptic fast waves in the hemispheres, described earlier, were unchanged. Low-voltage 1 and 2 cycle sine waves were obtained from a small area in the middle of the skin flap. No phase reversal was found" (Fig. 4*d*). Records were repeated at weekly intervals until his discharge on September 15th, 10 months after the injury and 2 months after the fit. In all 10 sets of records were obtained. No further fits had occurred up to a year after the operation.

COMMENT.—This is a case of a penetrating wound of the brain without any evidence of general *commotio cerebri*. There was only transient disturbance of visual function. One e.e.g. recorded 4 months after the injury, when the patient was symptom and sign free, showed bilateral generalized fast activity of an epileptic type with abnormal slow waves in the neighbourhood of the injury. There was no focal epileptic disturbance around this area. Traumatic epilepsy began about 8 months after the injury and a large cortical scar was completely removed shortly after this. Serial e.e.gs. taken at frequent intervals before and after operation failed to show any subsidence in the epileptic activity which had been present before the fit. The epileptic process which had become generalized was not modified by removal of the causal abnormal brain.

Observation of the progress of this kind of

case suggests that, as occurred in Case 2, when e.e.g. evidence of epileptic activity transcends the neighbourhood of local cerebral damage and becomes widepread it is likely to persist and not to be permanently affected by removal of the damaged and scarred brain which in some way initiates the epileptic processes. It seems, however, that when the damaged brain is completely removed before the process begins, and the e.e.g. recorded from the affected neighbourhood is normal, subsequent dysrhythmia is unlikely to appear. The evidence for this statement is obtained from many cases of penetrating brain injury in which toilet and debridement has been adequate. These cases, operated on when in the Military Hospital (Head Injuries) and 1st Canadian Neurological Hospital, have been investigated at varying intervals after the toilet, and it is very common to find no evidence of focal abnormality in the e.e.g. It seems that simple absence of brain tissue with slight gliosis is insufficent to give rise either to demonstrable slow activity or to a disturbance in the e.e.g. of the epileptic type. These two observations seem important in relation to the surgical management of traumatic epilepsy.

Discussion

Walter *et al.* (1937) pointed out that the e.e.g. was more likely to show abnormality in idiopathic epileptics than in those with symptomatic epilepsy, and they were unable to find any dysrhythmia in 4 cases of traumatic epilepsy. They also observed that the occurrence of abnormality in the e.e.g. of epileptics decreased with age. Jasper, Kershman and Elvidge (1940) and Gibbs, Merritt and Gibbs (1943), using a monopolar technique, found foci of abnormality so frequently in patients with traumatic epilepsy, contrasted with idiopathic epilepsy, that it seemed reasonable to conclude that a focal disturbance indicated a gross anatomical cause for the epilepsy. Paradoxically, although the e.e.g. can be used in this way to demonstrate unsuspected gross causes of epilepsy, it also indicates a fundamental unity between idiopathic and symptomatic epilepsy, and exposes the artificial nature of this division, for the pattern of the dysrhythmias seen are identical in the two conditions.

The immediate disturbances in the e.e.g. which result directly from cerebral injury caused by trauma, a tumour or any other agent, and those which arise subsequently and which are so frequently associated with epilepsy, can often be clearly differentiated. The directly acquired disturbances which were originally described by Berger (1929) and which were called " delta " waves by Walter (1937), have a frequency of the order of ½ to 3 a second and are found in the neighbourhood of the damaged brain. When, however, all the hemisphere is in a state of dysfunction, as it is after concussion, the disturbance is widespread (Williams and Denny-Brown, 1941). The dysrhythmia caused by these slow waves is reversible, for it subsides with recovery, and the voltage, period, persistance and area of origin of the abnormal waves are directly related to the degree of cerebral dysfunction.

The secondarily acquired dysrhythmias which arise as an indirect result of the cerebral insult and which are the subject of this paper, have many characteristics by which they can be recognized. Their most fundamental quality is that their relationship to the injury is indefinite. Their morphological characteristics—voltage, period, distribution and number—do not reflect the severity of the injury; they may arise long after the immedate effects of injury have subsided; they may arise from points in the hemispheres remote from the damaged area; and their actual presence does not depend upon the severity or kind of injury alone. Another fundamental distinction between the primary and secondary effects which may arise in the e.e.g. as a result of cerebral damage is that of persistence in time. Whereas the direct effects are usually reversible and transient, subsiding with clinical recovery, the delayed indirect effects when they arise are usually irreversible and persistent.

The form of the indirectly acquired dysrhythmias depends, of course, upon the characters of the waves of which they are constituted. These waves tend to have a high voltage in relation to their period; their frequency ranges from 2 to 3 a second upwards; there is great variability both in frequency and amplitude so that the record gives an appearance of instability; they tend to be episodic in their occurrence and to be linked into wave complexes of easily recognized form; they are often symmetrical or widespread throughout the hemispheres although they may be propagated from the zone of damaged brain over long periods of time; and they respond to physiological changes such as visual stimulation or changes in the blood Ph. It is evident then that a distinction is being made, and can usually be made as a result of a single examination of the e.e.g. records, between the primary effects of brain damage, which are reversible and transient, and secondary effects which are irreversible and persistent. This distinction has been made in presenting the results of the present investigation.

It will be recognized that the secondary changes may be indistinguishable from the disturbances seen in the e.e.g. of patients with idiopathic epilepsy and with other behaviour disorders which appear to arise mainly from inborn, constitutional causes. The initiation of this kind of disturbance after brain damage certainly does not depend upon the damage alone. Other factors, some of which precede the trauma, are responsible. That the age of the patient is one of these factors is shown by an interesting discrepancy between the present observations and those of Gibbs, Merritt and Gibbs (1943). Whereas Gibbs and his colleagues show several illustrations of " wave and spike " complexes which occurred in children with traumatic epilepsy, the present writer had formed the opinion that this phenomenon was not encountered in symptomatic epilepsy The explanation seems to lie in the age groups, since none of the subjects of this present investigation are

under 18 years, and children are rarely examined. Further evidence that other potent causes are at work is found in the observation that there is no obvious relationship between the nature or the site of brain damage—whether the injury is caused by trauma, tumour, infection or toxæmia—and the kind of epileptic disturbance which may result.

There is much histological evidence that the widespread pathological changes which occur in association with idiopathic and symptomatic epilepsy are similar, but, as Muskens (1928) concludes in his careful appraisal of the evidence, it is impossible to decide whether these well-recognized areas of neuronal degeneration and glial overgrowth reflect the result or the cause of long-standing epilepsy. The same is unfortunately true of the dysrhythmias seen in the e.e.g. It seems, in fact, that the purely descriptive approach to the electrical changes in epilepsy has reached the same point as the histological, a point which is far short of an understanding of the underlying disturbance which constitutes epilepsy, and further advances will depend on experimental methods.

Although the electrical disturbances associated with epileptic activity are similar whatever may be the precipitating cause of the illness, idiopathic and traumatic epilepsy differ in the frequency of the occurrence of the episodic discharges as well as in the site of origin of the discharges. These differences have some value in diagnosis.

When changes which have been described as larval attacks are seen at an interval after injury, epilepsy is virtually certain to supervene. When less distinct paroxysmal discharges occur there is more than an even chance of traumatic epilepsy, but in all other cases the e.e.g. gives no guide as to the probability of epilepsy following cerebral injury.

Summary

Electroencephalograms have been recorded in large groups of patients with idiopathic epilepsy, traumatic epilepsy and with head injuries without epilepsy, as well as in a large control group of normal subjects. e.e.gs. were also obtained before and after the onset of traumatic epilepsy in a small group of subjects.

The records in these groups have been compared, and the results obtained show that larval epileptic outbursts in the e.e.g. are invariably associated with overt fits, while less well-defined paroxysmal outbursts are also frequently associated with fits. These disturbances, which occur in 25 per cent. of traumatic epileptics compared with 56 per cent. of idiopathic epileptics, may be used with other signs to predict the likelihood of traumatic epilepsy. In other cases of head injury when these changes are absent, the e.e.g. offers no such help. The likelihood of epilepsy supervening when these disturbances are present has been examined in closed and penetrating head injuries.

The records made before and after the onset of fits show that the characteristic episodic changes often appear in the e.e.g. before the onset of traumatic epilepsy.

The site and nature of the disturbances in traumatic epilepsy are described. A distinction is made between the immediate and direct effects of trauma upon the e.e.g., and the remote, indirect and persistent effects which are usually associated with epilepsy. The results are compared with those of other workers and are used in discussing the relationship of symptomatic to idiopathic epilepsy.

I am grateful to the Medical Officers whose patients have been used for this enquiry, and to A/S/O J. K. Reynell for her technical help. The apparatus used for many of the earlier cases was kindly lent to the Royal Air Force by the National Hospital, Queen Square.

Bibliography

Ascroft, P. B. (1941). *Brit. mcl. J.*, **1**, 739.
Berger, H. (1929). *Arch. f. Psychiat.*, **87**, 527.
Finley, K. H., and Dynes, J. B. (1942). *Brain*, **65**, 256.
Gibbs, F. A., Gibbs, E. L., and Lennox, W. G. (1943). *Arch. Neurol. Psychiat.* (*Chicago*), **50**, 111.
Gibbs, E. L., Merritt, H. H., and Gibbs, F. A. (1943). *Ibid.*, **49**, 793.
Golla, F., Graham, S., and Walter, W. G. (1937). *J. ment. Sc.*, **83**, 137.
Heppenstall, M., E. and Hill, D. (1943). *Lancet*, i, 261.
Jasper, H. H., Kershman, J., and Elvidge, A. (1940). *Arch. Neurol. Psychiat.* (*Chicago*), **44**, 328.
—— and Kershman, J. (1941). *Ibid.*, **45**, 903.
—— and Penfield, W. (1943). *Am. J. Psychiat.*, **100**, 365.
Muskens, L. J. J. (1928). *Epilepsy—Comparative pathogenesis, Symptoms and Treatment.* London, Chapter 13.
Walter, W. G. (1937). *Proc. roy. Soc. Med.*, **30**, 579.
Williams, D. (1941 (a)). *J. Neurol. Psychiat.*, **4**, 107.
—— (1941 (b)). *Ibid.*, **4**, 131.
—— and Denny-Brown, D. (1941). *Brain*, **64**, 223.
—— (1944). *Ibid.*, **67**, 10.
—— and Sweet, W. (1944). *Lancet*, ii, 430.

THE RELATION BETWEEN THE EFFECTS OF THE BLOOD SUGAR LEVELS AND HYPERVENTILATION ON THE ELECTROENCEPHALOGRAM

BY

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THE frequency and amplitude of the rhythms seen in the electroencephalogram (e.e.g.) are altered greatly in certain subjects when alkalosis is induced by over-breathing. The alteration may take two forms: first, an accentuation of abnormal rhythms present in the resting e.e.g., and secondly, a production of rhythms not previously apparent. These effects may occur alone, or together, and in each case the alteration is most marked in the slower frequencies, that is, those of less than 8 c./sec. Fast rhythms, that is, those of rate greater than 14 c./sec., are rarely accentuated or produced on over-breathing, except when they occur as a component of a specific complex, such as the wave and spike which is produced in some epileptics. The most common response on hyperventilation is the appearance of 2–3 c./sec. rhythms of high amplitude, often called delta rhythms, which are seen first in the frontal regions and later, though in less size, posteriorly. The occurrence of these slow rhythms at 2–3 c./sec. as a result of hyperventilation is generally referred to as " instability " of the e.e.g. on hyperventilation.

It has been thought that a delta rhythm easily elicited by, and persisting for more than 20 seconds after the cessation of, hyperventilation may be an epileptic phenomenon. Evidence has accumulated to show that this instability or easy elicitation of delta rhythms is not peculiar to epileptics, and is found in a variety of other conditions. Thus it is a normal response in children. Brill and Seideman (1941) found that 40 per cent. of normal children between the ages of 4 and 6 years produced delta waves on hyperventilation, 9 per cent. between 10 and 12, and slightly more than 9 per cent. in the 12 to 13-year period. Williams (1941), in a survey of 900 subjects including epileptics, psychoneurotics, those with post-concussive states and controls, found that 75 per cent. of those with an abnormal resting e.e.g. produced delta waves on hyperventilation. In a group of post-traumatic cases 45 per cent. of those with abnormal resting e.e.gs. were found to show instability on over-breathing (Heppenstall and Hill, 1943), and a correlation with the age at which the injury occurred was demonstrated; the younger the person at the time of injury the more likely was the instability, or appearance of delta rhythms, to occur. Hill and Watterson (1942) in a study of a group of psychopathic persons found that of those with abnormal resting e.e.gs. about 70 per cent. showed instability on hyperventilation. Still further evidence that the production of delta waves on over-breathing is not specific to epilepsy is given by the work of Rubin and Turner (1942*a*) showing that such waves occurred in 55 per cent. of normal controls and 3 per cent. of a group of schizophrenics.

An abnormal resting e.e.g. is more frequently associated with the appearance of delta rhythms on over-breathing than is a normal resting e.e.g. At this unit, however, several controls who had no history of nervous and mental disease and who had normal resting e.e.gs. have been observed to produce delta rhythms on over-breathing. Osgood and Robinson (1940) found among a group of institutional epileptics, who had had no fits for 5–30 years, that 10 who had normal resting e.e.gs. produced delta waves on over-breathing.

It thus appears that the presence of delta waves on hyperventilation cannot be of value as a test for epilepsy unless specific complexes, such as wave and spike, are released. The production of 2–3 c./sec. rhythms seems to occur in varying degree in all groups studied, but no account has been taken of the physiological state of the subjects. By varying the level of sugar in the blood the response to over-breathing may be modified; even slight changes in blood sugar level may have a remarkable effect. Thus in a case reported by Hill, Sargant, and Heppenstall (1943) delta rhythms were elicited by hyperventilation at a blood sugar level of 97 mg. per cent., but not at 113 mg. per cent.; in the same case lowering the blood sugar level with intravenous insulin to 44 mg. per cent. caused the slow rhythms to appear one minute earlier during over-breathing than at a higher level of 88 mg. per cent. Studying cases of Addison's disease, Engel and Margolin (1942) found that in a fasting patient over-breathing easily elicited delta waves, but 30 minutes after the oral administration of glucose even 4 minutes of over-breathing did not alter the record from its

* Receiving a Rockefeller grant.

resting state. Rubin and Turner (1942*b*), in a series of experiments on a schizophrenic patient, found that the delta activity produced on hyperventilation decreased as the blood sugar level increased and considered 120 mg. per cent. to be the critical level. Suppression or reduction of delta waves was noticed by Liberson and Strauss (1941) after intravenous glucose injection. This effect was greater in adults and adolescents than in children.

Davis and Wallace (1942) and Engel *et al.* (1944) stressed the need for knowing or controlling the blood sugar value when using over-breathing as a test of stability of the e.e.g. even though the blood sugar level was not thought to be the only factor determining the production of slow cortical rhythms. The latter authors made the interesting observation that the increased stability of the e.e.g. to hyperventilation at high compared with low blood sugar levels was not due to the raised blood sugar level preventing the same degree of alkalosis being attained. Brazier, Finesinger, and Schwab (1944) studied the relationship between hyperventilation and blood sugar levels in a group of 45 normal controls. Their results led them to suggest that the appearance of delta waves for 5 per cent. of the second minute of hyperventilation at a blood sugar level above 130 mg. per cent. be regarded as abnormal. Their subjects over-breathed at the rate of 30 respirations per minute with depth adjusted according to body weight. Only the potentials from the occipital cortex were examined.

Therefore, the facts already known are:

(*a*) that there is a relationship between blood sugar level and the appearance of delta waves in the e.e.g. on over-breathing;

(*b*) that delta waves have been observed to occur during alkalosis induced by over-breathing at fasting blood sugar levels in a wide variety of abnormal states and in normal people, that is, those with no history of nervous and mental disorder;

(*c*) that raising the blood sugar above fasting levels has been shown to prevent the appearance on over-breathing of delta waves in a schizophrenic and in normal people.

The question that arises is whether raising the blood sugar level, in all subjects observed to show instability on over-breathing at fasting blood sugar levels, will prevent instability or appearance of delta rhythms on hyperventilation. If this is not the case there may be a particular clinical group in which, when the blood sugar level is raised, over-breathing may still produce delta waves. Under these circumstances it should be possible to indicate a simple test which could be used as a routine in electroencephalography to isolate certain clinical groups. The object of this work, therefore, has been first to find a suitable method for observing and assessing the effect of blood sugar level on the elicitation of delta rhythms on over-breathing and secondly, to study the e.e.g. during over-breathing at raised blood sugar levels in various clinical conditions.

Method

A three-channel Grass amplifying unit with ink-writing recorders was used. The e.e.g. was taken with the patient sitting erect and recorded simultaneously from four silver electrodes covered with saline pads and spaced 6 cm. apart in the frontal, precentral, postcentral, and occipital regions. The patient fasted for at least 4 hours before the test. After a short resting recording, a sample of blood was taken from the finger and the patient over-breathed at 20 respirations per minute for 3 minutes. A record was taken throughout hyperventilation and continued until the e.e.g. had returned to the resting state. The patient was given glucose, 50 gm. in water, by mouth, and the previous procedure carried out either once or twice at approximately 20-minute intervals depending on whether after the first interval the e.e.g. remained unaltered on hyperventilation. The blood sugar was estimated by the Hagedorn-Jensen method.

The ideal method for expressing the gradual change to predominantly slow rhythms during over-breathing is the use of an automatic frequency analyzer (Grey Walter, 1943). Unfortunately, when these experiments were carried out an analyzer was not available and a method of visual counting had to be used. The rhythms counted were divided into two groups, those of 2–3 c./sec. and those of 4–6 c./sec. Two periods were analyzed, 30 seconds before and 30 seconds after cessation of hyperventilation. As slow rhythms, particularly those in the 4–6 c./sec. band occurred in the resting record in most cases, it was necessary to eliminate these rhythms as far as possible when assessing the over-breathing response. The majority of slow rhythms in the resting e.e.gs. occurred with amplitude less than 75 μv., therefore this value was taken as the amplitude below which no slow frequency was counted. The slow rhythms elicited by hyperventilation usually appeared with amplitude greater than 75 μv. and the use of this value as the lower limit did not exclude changes obviously due to hyperventilation. A count was made of the slow rhythms, in each of the three leads, during the 30-second periods, and the time during which these slow rhythms were present was expressed as a percentage of the 30 seconds. The figures given in Table I are an average of the values for the three leads. Table I shows the percentage time occurrence of the slow rhythms, 2–3 and 4–6 c./sec., having amplitude greater than 75 μv. in period (*b*) 30 seconds before and period (*a*) 30 seconds after cessation of hyperventilation at fasting and raised blood sugar levels.

Results

The subjects examined (71) included epileptics (22), neurotics (17), psychopathic personalities (17), those with post-traumatic states (9), and 6 others who cannot be included in the above groups. All have been chosen because at fasting blood sugar levels the e.e.g. changes to predominantly slow rhythms during hyperventilation. In Table I the results are grouped according to the clinical classification.

Examination of the results as a whole shows that raising the blood sugar level markedly decreases the amount of slow rhythms present during over-breathing. In some cases countable slow potentials are still elicited at the raised blood sugar levels while in others the e.e.g. remains unchanged from the resting state. In the 71 subjects examined there appear to be two types, those in whom raising the blood sugar level prevents the appearance of slow rhythms, called for simplicity group 1, and those in whom slow rhythms still appear, called group 2.

TABLE I

Case No.	Age	Resting, E.E.G.	Blood sugar, mg. per cent. ..	Percentage time occurrence											
				<110				110–130				>130			
			Frequency, c./sec. .. .. Period counted	2–3		4–6		2–3		4–6		2–3		4–6	
				b	a	b	a	b	a	b	a	b	a	b	a
			Epilepsy												
5009	36	−		15	10	1	0	10	10	2	1	6	1	3	0
5006	23	+		23	22	9	3	.....		.....		6	0	11	5
5355	24	++		20	+	17	+	.....		.....		6	3	4	2
5568	26	+		.....		.....		8	1	6	3	6	0	8	1
645	20	++		36	21	15	7	5	8	4	3	4	1	6	3
3085	29	+++		40	24	7	9	11	3	11	5	8	2	8	0
4578	20	+		26	13	10	5	.....		.....		5	2	7	4
4449	18	++		+	+	+	+	.....		.....		3	2	0	0
5201	29	+		44	43	4	3	16	13	6	5	9	1	2	1
5760	29	+++		21	9	4	2	.....		.....		4	1	1	0
5287	19	+		21	21*	4	4*	12	2	2	1	4*	3	2*	2
5041	20	+		38	19	1	0	4	0	1	0	8	3	2	0
5239	24	+		17	9	1	1	5	3	0	0	3	1	0	0
4106	21	++		2*	3	6*	6	.....		.....		11	5	3	2
1459	35	++		19*	19*	1*	1*	.....		.....		4*	3*	1*	1*
5667	20	+		19	11	4	3	.....		.....		8	1	3	1
3516	20	++		+	+	+	+	.....		.....		12	9	1	0
5271	27	+		20	16	7	4	.....		.....		5	2	2	1
521	18	+++		.....		.....		spike and wave				spike and wave			
5191	17	++		spike and wave				.....		.....		spike and wave			
5767	18	+		spike and wave				.....		.....		spike and wave			
5172	38	++		spike and wave				.....		.....		spike and wave			
			Neurosis												
5351	19	+		9	3	1	0	.....		.....		0	0	0	0
4801	18	+		37	8	5	2	.....		.....		0	0	0	0
4800	18	+		+*	+*	+*	+*	.....		.....		0	0	0	0
4305	24	−		16	10	6	2								
				0	0	0	0								
5589	34	−		.....		.....		4	2	1	0	0	0	0	0
5195	21	−		72	21	0	0	12	3	0	0	0	0	0	0
4038	32	+		23	15	1	2	13	1	0	0	0	0	0	0
5306	21	+		13	2	3	2	0	0	0	0				
4506	26	+		7	8	3	2	0	0	0	0				
5694	29	+		27	9	0	0	.....		.....		0	0	0	0
5174	31	++		7	13	3	7	0	0	0	0				
5117	20	+		7	11*	1	2*	.....		.....		0	0	0	0
4475	39	−		20*	11*	3*	0*	0	0	0	0				
4767	25	+		9	6	7	3	0	0	0	0				
4305	30	+		33	3	12	2	0	0	0	0				
5595	32	−		9*	5	0*	0	0	0	0	0				
4576	20	+		23	16	0	0	0	0	0	0				
			Psychopathy												
5017	27	−		+*	0	+*	0	0	0	0	0				
3628	22	+		19*	12	4*	3	.....		.....		0	0	0	0
5072	21	+		26	30	3	2								
				0	0	0	0								
3426	20	+		14	0	3	0	0	0	0	0				
4387	26	+		21	19	6	7	0	0	0	0				
4868	21	−		16	12	3	1	.....		.....		0	0	0	0
4329	20	+		45	31	6	5	0	0	0	0				
3926	39	+		4*	7	1*	1	4	4	0	1	0	0	0	0
5166	30	−		.....		.....		12	5	2	0	0	0	0	0
3468	19	++		11	7	1	1	.....		.....		1	0	2	0
6007	20	+++		25*	15*	1*	0*	9	2*	4	1*				
5656	20	++		+	+	+	+	.....		.....		8	4	3	0
5360	33	++		11	6	2	2	.....		.....		4	4	2	1
5137	37	+		20	44	2	2	25	10	1	1	8	4	1	0
5642	28	+		26	8	2	1	.....		.....		9	1	1	0
4147	21	++		12	4	4	0	.....		.....		13	3	0	0
5637	20	++		34	33	4	2	.....		.....		10	1	2	3

TABLE I—*continued*

Blood sugar, mg. per cent. ..			Percentage time occurrence							
			<110		110–130		>130			
Frequency, c./sec. .. .. Period counted			2–3 b a	4–6 b a	2–3 b a	4–6 b a	2–3 b a		4–6 b a	
Case No.	Age	Resting, E.E.G.								
			Post-traumatic states							
4351	26	+	11 10	0 0	1 0	0 0				
5486	39	+	10 20	2 0	0 0	0 0				
5701	20	+	16 1	4 0	0 0	0 0				
5039	26	+	9 24	3 1	.....	.....	0	0	0	0
4429	29	−	10* 3	3* 2	0 0	0 0				
3585	40	+	21 15	5 2	7 5	3 2	0	0	1	0
5682	23	+	16 8	0 0	.....	.....	8	3	0	0
4213	22	−	30 21	9 5	9 5	2 1				
4230	25	+	27 12	1 0	4 3	1 0	7*	0	0*	0
			Miscellaneous							
3321	26	+	14 15	0 1	18 16	1 0	9	5	0	0
5135	20	+	31 9*	5 4*	.....	.....	5	1	5	2
4155	31	−	5 1*	0 1*						
			0 0	0 0						
5290	20	++	12 3	1 1	.....	.....	0	0	0	0
4791	21	+	18 25	4 3	0 0	0 0				
1219	26	+	35 30	8 7	.....	.....	8	7	4	2

Classification of resting E.E.G.: −, normal. +, mildly abnormal. ++, moderately abnormal. +++, severely abnormal.

* Value low due to masking by movement and muscle artefacts. Where a + sign is given instead of an actual amount for the percentage time occurrence the recording was not taken with the electrodes in the specified positions.

In the first group both the 2–3 and the 4–6 c./sec. rhythms elicited at fasting blood sugar levels on over-breathing may be prevented from appearing both during and immediately after hyperventilation if the blood sugar level is raised. Since sufficient time for the system to recover from over-breathing must be allowed between tests and since, in most cases, the blood sugar level rises rapidly after the ingestion of glucose the actual value of the blood sugar at which the response to over-breathing becomes stable cannot be determined. In this first group 20 subjects have been found in whom instability on hyperventilation has been abolished by raising the blood sugar level to less than 130 mg. per cent. In the other 15 subjects the blood sugar level rose to above 130 mg. per cent. before the second hyperventilation was done; opportunity to repeat the test to determine whether the response would have been stable at a much lower level did not occur. However, the available results suggest that if raising the blood sugar above fasting levels will stabilize the response to hyperventilation, it will do so at a relatively low value. Other workers (Davis and Wallace, 1942; Rubin and Turner, 1942*b*; and Brazier, Finesinger, and Schwab, 1944) have suggested that 120–130 mg. per cent. is the critical blood sugar level.

In the second group the final hyperventilation test has been made in 9 subjects with blood sugar values between 130 and 150 mg. per cent., and in 25 subjects with values between 150 and 210 mg. per cent. Although they may belong to this group, 2 subjects (4213 and 6007) have not been included, as the final blood sugar level has not been sufficiently high to give a conclusive result. In 4 subjects over-breathing produced spike and wave complexes. These complexes are composed of numerous frequencies including those slow rhythms counted and presented in Table I. Therefore, since raising the blood sugar level even as high as 200 mg. per cent. does not prevent the spike and wave complexes being released, these 4 subjects have been included in the second group. It would be interesting to study more cases in which spike and wave complexes are released by hyperventilation since the findings in the above-mentioned 4 subjects are not in agreement with those of Williams (1941), who states that the wave and spike pattern released on over-breathing may be inhibited by raising the blood sugar level.

Modification of all the slow rhythms elicited on hyperventilation does not apparently take place to the same extent when the blood sugar level is raised since whereas the 2–3 c./sec. rhythms are invariably decreased in amount, the 4–6 c./sec. rhythms may remain in similar quantity or even be increased. This effect may be actual or may be due to the inability of the eye to see the 4–6 c./sec. potentials in the presence of high amplitude slower rhythms. The latter view is more probable, and it seems unjustifiable to discuss the 4–6 c./sec. rhythms until an

improved analysis of the e.e.g. records is available. In group 2, 2–3 c./sec. rhythms of more than the critical size of 75 μv. occur at blood sugar levels above 130 mg. per cent. in every case in period (*b*), and in the majority of cases in period (*a*); the lower times of occurrence in period (*a*) compared with those in period (*b*) are due to the fact that the e.e.g. has usually returned to the resting state before the thirty seconds have past.

Having divided the cases into 2 groups the possibility of a correlation between the groups and other factors arises. The three factors that have been investigated are age, degree of abnormality of the resting e.e.g., and the clinical diagnosis. The results are given in Tables II and III.

TABLE II

Group	Age		Resting E.E.G.	
	<20	>20	−, +	++, +++
1	9	26	33	2
2	14	20	18	16

TABLE III

Clinical diagnosis	Group 1	Group 2	Doubtful
A. Epilepsy	0	22	—
B. Neurosis	17	0	—
C. Psychopathy:—			
Aggression	2	3	1
Others	7	4	—
D. Post-traumatic states..	6	2	1
E. Miscellaneous ..	3	3	—

It is known that there is a relation between age and instability of the e.e.g. to hyperventilation in children and adolescents. The e.e.g. becomes more stable as the age increases. If this change continues in adults the difference between groups 1 and 2 might therefore be due to age. In order to test this possibility the subjects in groups 1 and 2 have been divided into those less than 20 years old and those more than 20 years old. No correlation between age and the group into which a subject falls can be shown, see Table II [$x^2=0{\cdot}76$, P lies between 0·5 and 0·3].

In order to see whether a relation exists between the group into which a subject falls and the nature of that subject's resting e.e.g., four classifications of the resting e.e.g. have been used, normal and mildly, moderately and severely abnormal. The cases have been divided between the normal and mildly abnormal on the one hand and the moderately and severely abnormal e.e.gs. on the other. The results of this division, given in Table 2, show that the degree of abnormality of the resting e.e.g. is a significant factor in determining into which group a subject may be expected to fall. Thus, where a resting e.e.g. is more than mildly abnormal, and the response on hyperventilation is unstable at fasting blood sugar levels, there is a great probability that the response at raised blood sugar levels will also be unstable. The probability is less that a normal or mildly abnormal resting e.e.g. will be associated with stability on over-breathing at raised blood sugar levels. A degree of cortical instability may therefore be revealed which is unexpected from the nature of the resting e.e.g.

Before considering groups 1 and 2 in relation to the clinical diagnosis a description of the case material, summarized in Table III, is given. Group A consists of 22 epileptics including service patients, civilian out-patients of this department, and a few patients from an epileptic colony. The ages vary from 17–38 years, giving a mean of 24·2. The majority have had more than one type of fit and have an associated personality disorder. In 12 subjects fits have developed within the last year, and in the remainder have been present for several years or since birth. One subject suffered a minor head injury since the onset of fits and another (3085) is considered to be suffering from traumatic epilepsy. Group B consists of 17 neurotics with ages varying from 18–39 years, mean 25·8, and includes patients showing anxiety or hysterical reactions. Slight cerebral trauma has occurred in 4 subjects (5517, 5351, 5595, and 4035) and moderate trauma in one (4801), whose clinical condition is not attributed to the injury. A history of epilepsy in a brother is alleged in 2 subjects (4801 and 5589). Group C consists of 17 patients with psychopathic personalities and ages varying from 19–39 years, mean 24·9. These 17 patients form a rather mixed group and are not clearly divisible into those who are predominantly aggressive and those who are predominantly inadequate, although 6 belong clearly to the former class (4171, 5360, 5017, 6007, 5642, and 4329). There are 3 cases of perverse sexuality (4171, 5166, and 3926), one of which (4171) is predominantly aggressive and therefore has been classified as such in Table III. One subject (3426) has been convicted for murder and another (5656) is a malingering psychopathic young woman charged with robbery. In 8 subjects there is a history of alleged concussion, and in one other, with a life-long personality disorder (6007), a head injury of moderate severity. There is a suggestion of epilepsy in the history of 3 of the subjects. One of these (4868) has had " sun-stroke " in England and at the time had " mainly fits." He has had no other epileptiform activity at any time. Another (4329) has had attacks of dizziness since aged 17, when he started boxing, and has fallen, hurting himself. The third (3468) fainted with incontinence as a child. In none of the 17 psychopathic patients has a family history of epilepsy been reported. Group D consists of 9 patients who have been examined because of symptoms following head injury, and all but one received the injury more than a year previously. The ages vary from 20 to 40, mean 27·8. There is a definite history of fracture in 3 cases (5683, 4213, and

4230). In 7 subjects the duration of post-traumatic amnesia was an hour or less, in one (5701) it was 15 hours and in another (5682) four days. No family history of epilepsy has been given in any of the 9 cases. A miscellaneous group, E, of 6 patients includes a patient with personality disorder following cerebrospinal meningitis (4155), a schizophrenic who has had fits on insulin treatment (1291), a life-long enuretic without spina bifida (3321), a patient with congenital alexia (4741), a service patient who has had a period of amnesia and was found wandering by the police in a London station (5135), and a sailor (5290), who is in prison for a very violent assault for which he has amnesia, yet with no history suggesting epilepsy.

Table III shows the distribution of the case material between groups 1 and 2 and the clinical diagnoses. It is seen that the neurotics fall exclusively into group 1 and the epileptics exclusively into group 2. The psychopathic patients are almost evenly divided, but there are too few of these patients for any significant factors to emerge. In subjects with post-traumatic states there is a strong tendency for those with mild head injuries to fall into group 1. Examination of many more patients is required before it is possible to investigate the relation between groups 1 and 2 and factors such as severity of injury and age at which the injury has been received.

There is, however, a clear correlation with the clinical diagnosis in the epileptic and neurotic groups, the most important point being that no habitual epileptic is found in group 1. In a case of doubtful diagnosis of epilepsy, therefore, if delta rhythms of voltage over 75 μv. appear on over-breathing with a blood sugar level of above 130 mg. per cent. the probability is markedly increased that the patient is an epileptic, irrespective of the nature of the resting e.e.g.

Discussion

The results just described confirm the work of others that the appearance of slow rhythms on hyperventilation in certain people is greatly dependent on the blood sugar level and that there is a critical level at 120–130 mg. per cent. above which, in many cases (group 1), the response is stable.

The object of this investigation, as already stated, has been to find whether observation of the response to hyperventilation at raised blood sugar levels will help to single out any particular clinical condition since instability at fasting levels is found in both normal and a wide range of abnormal states. Instability on hyperventilation with blood sugar levels above 130 mg. per cent. has been found in all the overt epileptics in this series. There is unfortunately not sufficient data to indicate whether a person with a predisposition to epilepsy will react in the same way as the overt epileptics. If, however, the delta rhythms produced on hyperventilation in a given subject fail to occur when the blood sugar level is raised, the probability that this subject suffers from epilepsy is materially reduced.

Electro-encephalographic data has recently been put forward by Hill (1944) in support of the suggestion made in 1873 by Maudsley that a close relation exists between epilepsy and psychopathic aggression. If this relationship is accepted then the number of subjects in group 2 who have epilepsy in one form or another is increased and the probability that a group 2 response indicates epilepsy is correspondingly greater. Not sufficient is known of the group 2 cases who are not habitual epileptics or aggressive psychopathic persons, to indicate any relationship of their clinical condition to epilepsy with the exception of the subject in whom fits occurred during insulin treatment and the subject who fainted with incontinence as a child.

The need for performing an over-breathing test at raised blood sugar levels in investigating suspected epileptics is obvious.

The persistence of slow rhythms for more than 20 seconds after the cessation of hyperventilation is usually taken as an " abnormal " response. In the group 2 cases at blood sugar levels above 130 mg. per cent. the persistence is invariably less than 20 seconds. Instability on hyperventilation at these levels has been shown to have a significant meaning the expression of which, therefore, requires another standard. A better method of evaluation is the appearance of slow rhythms—mainly the 2–3 c./sec. —of high amplitude in any region of the cortex during the period of hyperventilation. If this standard is used it is not always necessary to over-breathe for 3 minutes as the appearance of the slow rhythms is sufficient to indicate instability.

It is not practicable, at east in wartime, to give 50 gm. of glucose to every patient before an e.e.g. examination, and it is not often possible for the patient to have a meal at a suitable time beforehand. It is better, therefore, to take the resting record and to over-breathe with the patient fasting and if delta waves are elicited to raise the blood sugar and repeat the over-breathing. Instability at fasting levels may eventually be shown to have clinical significance, and data is not lost by using the method described. Whenever instability on hyperventilation is found the blood sugar value must be estimated.

The criticism may be made that the suggested test is too simple in that not sufficient account is being taken of other physiological factors which may be of importance. However, it is a procedure which is possible for most e.e.g. departments, and it does assist in sorting the degrees of cerebral instability shown on over-breathing. It is only a beginning of correlating the clinical condition with the knowledge to be gained by studying the e.e.g. under various physiological stresses.

Summary

1. The response of the e.e.g. to hyperventilation at raised blood sugar levels has been studied in 71 adult patients who showed instability of cortical rhythms when fasting. The subjects include patients with epilepsy (22), neurosis (17), psychopathic personality (17), and post-traumatic states (9).

2. Two types of reaction have been observed; one (group 1) in which raising the blood sugar level inhibits the appearance of slow rhythms and another (group 2) in which, although there is a reduction in amount, slow rhythms are still elicited with a blood sugar value of 130 mg. per cent. or above.

3. There is a significant relation between the degree of abnormality of the resting e.e.g. and the group into which a case falls. Those cases with a normal or mildly abnormal resting e.e.g. tend to fall into group 1 and those with a more than mildly abnormal resting e.e.g. into group 2.

4. All the neurotics are found in group 1 and all the epileptics in group 2.

5. Instability of the e.e.g. on hyperventilation at blood sugar values above 130 mg. per cent. is significant and its presence in these circumstances markedly increases the probability that the patient is an epileptic.

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References

Brazier, M. A. B., Finesinger, J. E., and Schwab, R. S. (1944). *J. clin. Invest.*, **23**, 319.
Brill, N. Q., and Seidemann, H. (1941). *Arch. Neurol. Psychiat.*, **46**, 374.
Davis, H., and Wallace, W. McL. (1942). *Ibid.*, **47**, 606.
Engel, G. L., and Margolin, S. G. (1942). *Arch. int. Med.*, **70**, 236.
Engel, G. L., Romano, J., Ferris, E., Webb, J. P., and Stevens, C. D. (1944). *Arch. Neurol. Psychiat.*, **51**, 134.
Heppenstall, M. E., and Hill, D. (1943). *Lancet*, **1**, 261.
Hill, D. (1944). *Proc. roy. Soc. Med.*, **37**, 317.
—— Sargant, W., and Heppenstall, M. E. (1943). *Lancet*, **1**, 526.
—— and Watterson, D. (1942). *J. Neurol. Psychiat.*, **5**, 47.
Liberson, W. T., and Strauss, H. (1941). *Proc. Soc. exp. Biol. Med.*, **48**, 674.
Maudsley, H. (1873). *Body and Mind.* London.
Osgood, R., and Robinson, L. J. (1940). *Arch. Neurol. Psychiat.*, **43**, 1007.
Rubin, M. A., and Turner, E. (1942*a*). *Ibid.*, **48**, 968.
—— (1942*b*). *Proc. Soc. exp. Biol. Med.*, **50**, 270.
Walter, W. G. (1943). *Electronic Engineering*, June, 9.
Williams, D. (1941). *J. Neurol. Psychiat.*, **4**, 257.

THE SCOPE AND LIMITATIONS OF VISUAL AND AUTOMATIC ANALYSIS OF THE ELECTROENCEPHALOGRAM

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Introduction

SINCE early in the history of the electroencephalogram (e.e.g.) it has been realized that the records are complex. That is to say, the rhythms in them are rarely simple harmonic oscillations and often have a number of components. The component oscillations may either bear some constant harmonic relation to one another or they may be entirely independent in their frequencies. The formation of complex waves from a number of simple sinusoidal components obeys certain well established physical principles. The purpose of this paper is to consider how these principles must affect the interpretation of an e.e.g. record. From this consideration two suggestions will result; first, that an application of the principles to the visual inspection and measurement of a record can materially increase the amount of information obtainable, and secondly, that there are certain types of change that occur in the e.e.g. that cannot be measured and assessed accurately except by a more elaborate form of analysis.

Analysis of the e.e.g. to separate its components has been made in the past in a number of ways. Mathematical analysis of a short length of record (Rohracher, 1937; Livanov and Petrova, 1938) is exceedingly tedious and not applicable to routine work. This method may, however, be of value in special cases, as it may give a degree of accuracy limited only by the quality of the original recording. Selective recording methods (Drohocki, 1938; Davis *et al.* 1938; Parr and Walter, 1943) are limited in scope as only a restricted part of the e.e.g. frequency band may be studied at one time. Until recently the only complete, accurate, and practical method described has been that due to Grass (Grass and Gibbs, 1938). In this method a special photographic record is made, a part of which is selected corresponding to thirty seconds of recording. This length of record is then analysed by an automatic electrical apparatus. A high degree of accuracy is obtained and the method has contributed much valuable information about the changes in the e.e.g. occurring in different physiological and pathological states. Unfortunately the length of record that may be analysed has to be limited. This, together with the need of a special record, probably accounts for the failure of this method to be readily accepted as a routine.

Recently a method has been described in which every ten seconds of record is analysed (Walter, 1943*a* and *b*). The analysis is automatically traced alongside the record in the form of a histogram, within ten seconds of the recording of the e.e.g. No extra labour is involved during or after the examination, and analysis during the entire period of recording becomes possible as a routine. It therefore seems desirable to decide what are the limitations of a visual inspection and measurement of an e.e.g record and when this fuller analysis is essential.

Study of a mixture of rhythms, such as make up the e.e.g., is difficult on account of the fact that the components rarely remain constant for long. To overcome this difficulty, and to demonstrate in a pure form the appearances that are produced when a number of rhythms are mixed, a method of synthesis of compound waveforms has been adopted. The method is an electro-mechanical one which allows a rapid alteration to be made in the frequency or amplitude of one or more of the components. By this means it is possible to mimic accurately the various waveforms that occur in the e.e.g. The ability to produce these effects without the distractions of the rapid changes occurring in the natural e.e.g., has proved of great value in visualizing the way in which a given wave in the e.e.g. may be expected to change in altered physiological conditions. In addition, a useful check on the accuracy of an analysis of the e.e.g. is available, for a synthesis of the components indicated, in the correct amounts, should in most cases produce a wave identical with that analysed.

Here it should be made clear that a synthesis of

this kind may equally well be made by graphical methods, and that for many years this has in fact been done for other purposes. An example of the valuable information that graphic synthesis may yield is given by the work of Gasser and Erlanger (1927) who used it to determine the components of the complex action potential wave in nerve. The graphic form of synthesis is, however, exceedingly tedious and is not practical as a demonstration method.

Method

Two or more oscillators giving simple harmonic oscillations of the same order of size and frequency as occur in the e.e.g. are used. These oscillators are connected to the inputs of a standard e.e.g. apparatus in such a way that one channel records the algebraical sum of the amplitudes of the oscillations and the other channels record the individual oscillations separately. Changes in a component and the resultant may thus be seen at the same time.

The oscillators used are of the photomechanical type. A selenium barrier-layer photoelectric cell is illuminated from a light source of fixed intensity and a suitably slotted disc interposed between the light and the cell. If the disc is rotated and the slots have the correct shape the amount of light falling on the cell will vary in a sinusoidal manner and the cell will produce a potential difference of sinewave form. The size of the potential difference may be altered by a potentiometer connected across the cell and the frequency of the oscillation changed by altering the rate of rotation of the disc. Oscillators using the photoelectric principle, also using capacities varied in size mechanically, have been described before (Schaffer and Lubsinski, 1931; Kurtz and Larsen, 1935). More recently an electronic method, suitable for use in the audible sound frequency band from 50 to 20,000 c./sec., but unsuitable for use at the low frequencies at which an e.e.g. apparatus works, has been described (Somerville, 1944).

In the earlier experiments when two or three separate oscillators have been used, some difficulty has been experienced in keeping them accurately in step, if constant frequency relations between several waves have been required. The results, however, have been so enlightening that a more complicated apparatus has been made. This apparatus, which is to be described elsewhere (Walter and Baldock, in press), will produce a harmonically related series of ten oscillations simultaneously. The individual generators are locked together on a common spindle and the frequency relations and phases of the oscillations may be adjusted and held absolutely constant.

Terminology

In the following description of compound waves it is assumed that the meaning of the terms Amplitude, Frequency, Cycle, and Sinewave oscillation are understood. For the last of these the terms simple harmonic oscillation and sinusoidal oscillation are also used. Other terms used may be less familiar and the sense in which they are used will be defined.

Harmonic Series.—When a series of sinusoidal oscillations have frequencies that are whole multiples of that of a single oscillation, which is called the fundamental, they compose part of a harmonic series. Thus, in a series in which the fundamental, or first harmonic, is 1 cycle per second (1 c./sec.), the second harmonic will have a frequency of 2 c./sec., the third of 3 c./sec., and so on. In a series with the fundamental 2 c./sec., frequencies of 4 c./sec. and 6 c./sec. would be called the second and third harmonics of the fundamental. The series need not necessarily be complete, any number of terms may be missing. For instance, two oscillations of frequency 20 and 22 c./sec. are the tenth and eleventh terms in a series with a fundamental of zero amplitude at 2 c./sec.

Phase.—The phase of an oscillation at any instant is considered to be that part of a complete cycle that has occurred since any arbitrarily chosen point in the cycle of oscillation. This is usually expressed as an angle; one complete cycle being 360°. Thus, if the zero position of a sinewave is taken as reference the oscillation is said to have completed 90° when the first peak is reached. Two oscillations are said to be in phase when they are passing through the same part of a cycle at the same time. When the peak of one oscillation coincides with zero of another they are 90° out of phase; when both oscillations leave their zero positions simultaneously, but in opposite directions, they are 180° out of phase.

Modulation.—When a single oscillation undergoes a rhythmical change in size it is said to be modulated in amplitude. If the amplitude is made to fluctuate between zero and twice the unmodulated size, the modulation is said to be 100 per cent. The percentage modulation is therefore an expression of the amount of fluctuation above and below a mean amplitude. For example, a 50 per cent. modulated wave would vary by plus and minus 50 per cent. of its mean amplitude.

Beats.—If the amplitudes of two sinusoidal oscillations are summed algebraically, the resultant will fluctuate in size at a rate equal to the difference in the frequency of the components. These periodic maxima and minima, which are called beats, are most obvious when the difference is a relatively small percentage of the frequencies of the components. The reason for the beating may be seen if two oscillations of 5 c./sec. and 6 c./sec. are considered. If these two oscillations have the same initial phase the sum of their amplitudes will be greater than that of either alone at this time. At the end of half a second, however, the 6 c./sec. oscillation will have completed 3 cycles; the 5 c./sec. oscillation will have completed only 2·5 cycles. The oscillations at this point will therefore be in opposite phase, and the amplitude of the resultant will be at a minimum. At the end of the full second, the cycle will be complete, and the waves will be in phase again. In the special case where the two oscillations have equal amplitudes, the resultant will fluctuate between zero and twice the size of either oscillation alone. Therefore, beating will always be most marked when the amplitudes of the two oscillations are nearly equal.

Results

A feature of certain types of e.e.g. record is the apparent cessation of a rhythm of 4–7 c./sec., in the parieto-occipital regions, when the alpha rhythm is produced on closing the eyes. This series of

events has been interpreted in two ways. Usually it has been considered that the 4–7 c./sec. rhythm has either speeded up to the faster rate and is itself a slow form of the alpha rhythm, or that the occurrence of the alpha rhythm inhibits the slower rhythm.

Analysis of the records, during the periods when the alpha rhythm is present and the slower rhythm apparently absent, gives an interesting result. It shows that in many cases the slow rhythm is quite unaltered in size, although it may not be seen in the record. This effect will be referred to as masking, and a rhythm which is shown to be present in a record by analysis, but which cannot be seen in the primary record, will be referred to as being masked.

To demonstrate this effect of masking of one rhythm by another, two rhythms, one of 8·5 c./sec. and one of 6 c./sec., have been combined in various sizes. The compound waves resulting are shown in Fig. 1. In (*a*) the two component rhythms are of almost equal amplitude, the resultant fluctuates in size from zero to twice the amplitude of either component, and the beats occur two and a half times a second. In (*b*) the 6 c./sec. and (*d*) the 8·5 c./sec. component is reduced in size by half. In (*c*) and (*e*) the same components respectively are reduced to a quarter of their original size. It immediately becomes obvious that the only frequency that may be counted directly in the resultant is that of the larger component.

When a rhythm, such as the resultant in Fig. 1 (*b*) is seen in an e.e.g. record its frequency, 8·5 c./sec., may be counted and the rate at which it fluctuates, 2·5 times a second, may be measured. The question then arises as to whether this fluctuation is due to the presence of a masked 6 c./sec. rhythm, or whether there is only an 8·5 c./sec. rhythm that is modulated 2·5 times a second. Single rhythms, modulated by fluctuating excitability, or degrees of synchronization of brain cells may occur. The outline of a wave that is sinusoidally modulated and of the resultant of two rhythms beating together, are different. To show this difference in its most obvious form frequencies higher than those normally found in the e.e.g. are used. In Fig. 2 are shown the effects of modulating a 50 c./sec. rhythm at 1·25 times a second and of beating between a rhythm of 50 c./sec. and another of 48 to 49 c./sec. In the records of modulation, Fig. 2 (*a*), (*b*), and (*c*), the top line indicates the extent and rate of modulation of the single frequency shown in the second line, and the third line shows the result of such modulation of the single frequency. The third line is not in this case a resultant of the algebraical summation of the top and second lines as is the case in the records of beating. The recording rate is such that while the individual waves

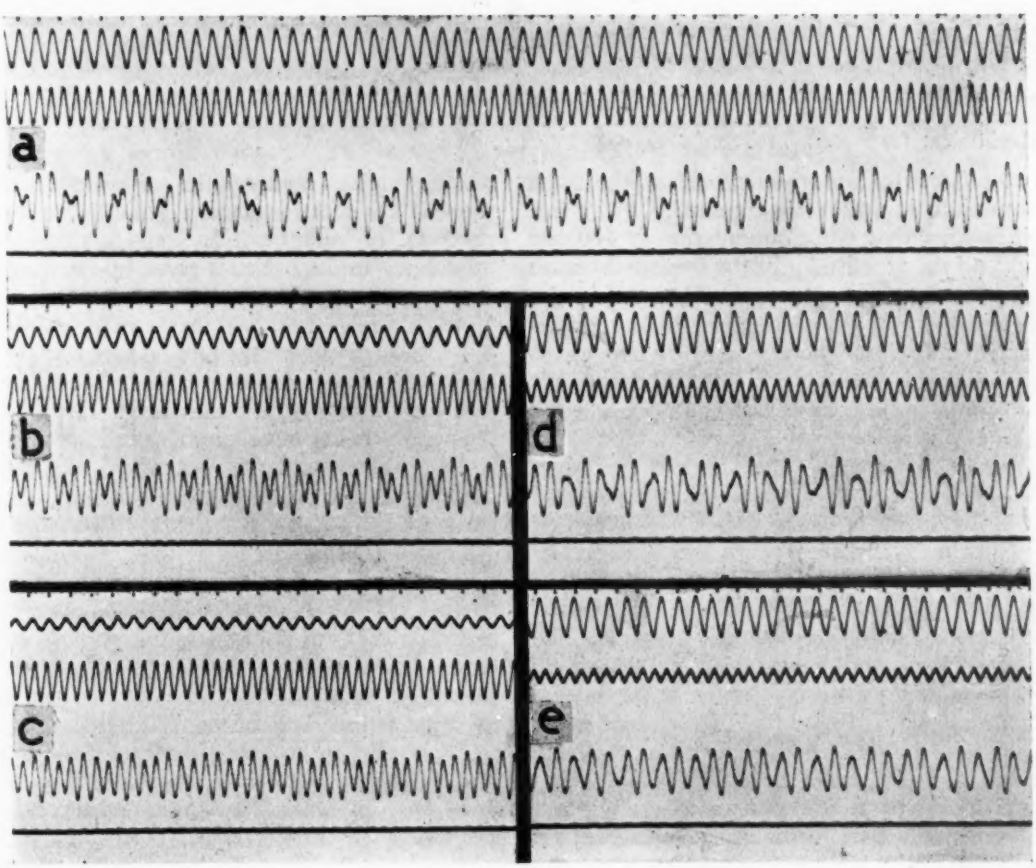

FIG. 1.—Cathode-ray oscillograph records showing *masking* of a smaller rhythm by a larger: (*a*) 8·5 c./sec. and 6 c./sec. equal; (*b*) 6 c./sec. reduced to 50 per cent.; (*c*) 6 c./sec. reduced to 25 per cent.; (*d*) 8·5 c./sec. reduced to 50 per cent.; (*e*) 8·5 c./sec. reduced to 25 per cent. In each record the upper trace shows the 6 c./sec. rhythm, the middle the 8·5 c./sec. rhythm, and the lowest the resultant of the two. Time marks at top of each record shows one-fifth sec.

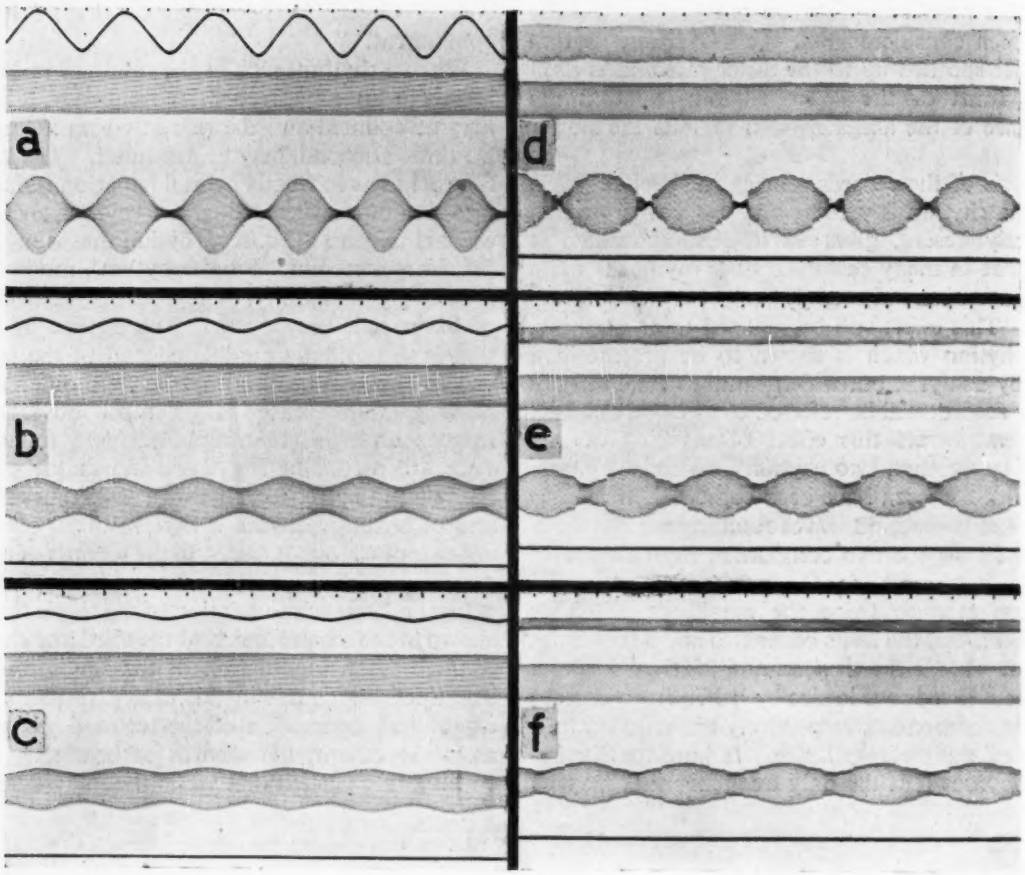

FIG. 2.—(*a*) 100 per cent. *modulation* of a 50 c./sec. rhythm at a frequency of 1·25 per sec.; (*b*) 50 per cent. modulation; (*c*) 25 per cent. modulation; (*d*) *beats* formed by two rhythms of 50 c./sec. and 49 c./sec. and equal amplitudes; (*e*) 49 c./sec. reduced to 50 per cent.; (*f*) 49 c./sec. reduced to 25 per cent.

of the 50 c./sec. rhythm are not resolved the beats and fluctuations in amplitude are clear. From this figure it is seen that when modulation is 100 per cent., (*a*), and the amplitudes of the two rhythms are equal, i.e. the beats are of maximal size, (*d*), the difference in the outlines of a single rhythm modulated in amplitude and the resultant of two waves beating is clear. When, however, the modulation is reduced to 50 per cent. or less, (*b*) and (*c*), and the amplitude of one of the beating waves to one-half or less of that of the other (*e*) and (*f*), it is no longer possible to distinguish between modulation and beating by the outlines of the waves produced. If the experiment is repeated using frequencies like those that occur regularly in the e.e.g., instead of the unnaturally high one of 50 c./sec., discrimination between the two effects is even more difficult. The results of such an experiment using a 10 c./sec. rhythm, modulated to varying depths at 2·2 times a second, are shown in Fig. 3 (*a*), (*b*), (*c*), and beats formed by an 8·5 c./sec. rhythm of fixed size and a 6 c./sec. rhythm of varied size, in Fig. 3 (*d*), (*e*), (*f*.) The use of these slow frequencies makes the outlines of the modulated wave and the beats discontinuous, with the result that it is no longer possible to tell the difference between them, even when the modulation is 100 per cent. and the beats are maximal, cf. Fig. 3 (*a*) and (*d*).

A particular instance of the importance of knowing whether a fluctuating rhythm is made up of two other rhythms, or whether it is a single rhythm that is modulated in the brain, is given by the diagnosis of deep tumours of the brain (Walter and Dovey, 1944). Here, a separation has to be made between the 4–7 c./sec. rhythms that often occur in the parieto-occipital regions and have already been mentioned, and the faster rhythms that occur farther back in the head. If a residual alpha rhythm of appreciable size is present with the eyes open, and cannot be inhibited by the usual measures, it may completely mask a small 4–7 c./sec. rhythm. Conversely, if the 4–7 c./sec. rhythms are larger than the alpha rhythm, it may be impossible to say whether or not the alpha rhythm has been inhibited on opening the eyes. The record in Fig. 4 (*a*), illustrates this point in a manner that simulates the e.e.g. more closely than the preceding records. In the resultant of the two rhythms, in line three of the record, it is not possible to count the rate or assess the size of the 8·5 c./sec. rhythm during the period, corresponding to "eyes open," when it is of small amplitude. When the 8·5 c./sec. rhythm is large, corresponding to an "eyes closed" period, it is not possible to assess the size or rate of the 6 c./sec. rhythm.

The effects of over-breathing may be given as another example of the occurrence of masking of

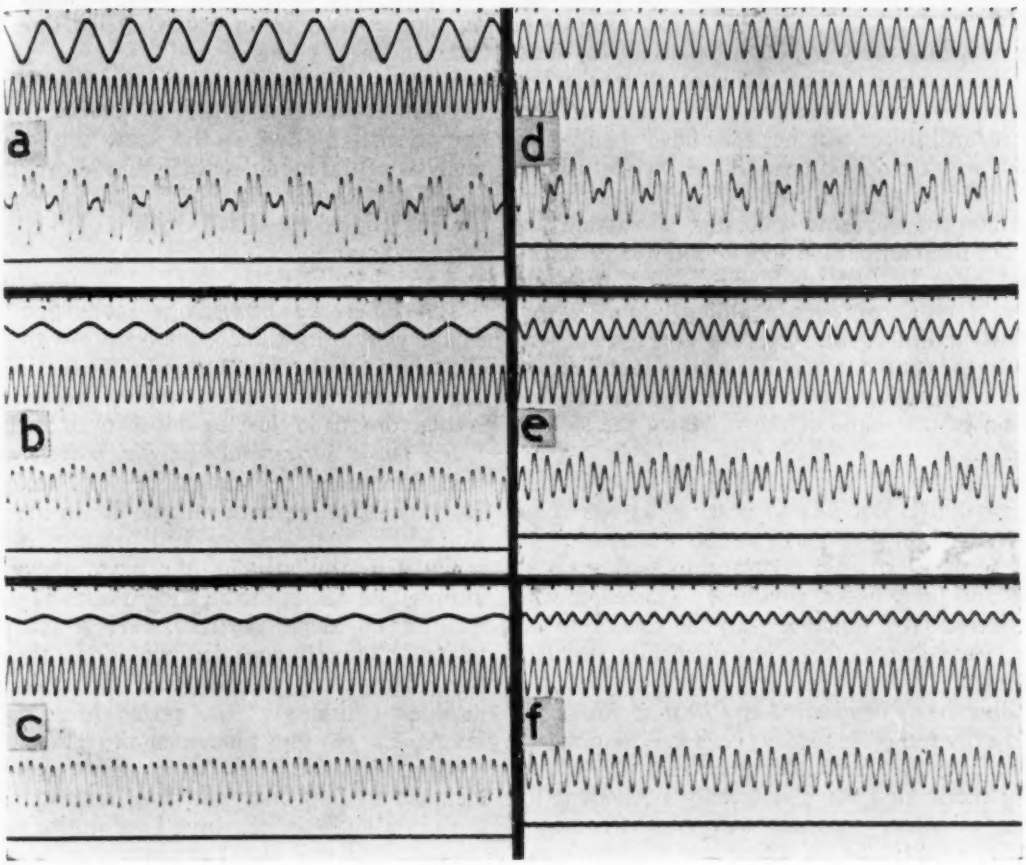

FIG. 3.—(*a*) 100 per cent. *modulation* of a 10 c./sec. rhythm at a frequency of 2·2 c./sec.; (*b*) 50 per cent. modulation; (*c*) 25 per cent. modulation; (*d*) *beats* formed between a rhythm of 8·5 c./sec. and one of 6 c./sec. of equal amplitude; (*e*) 6 c./sec. reduced to 50 per cent; (*f*) 6 c./sec. reduced to 25 per cent.

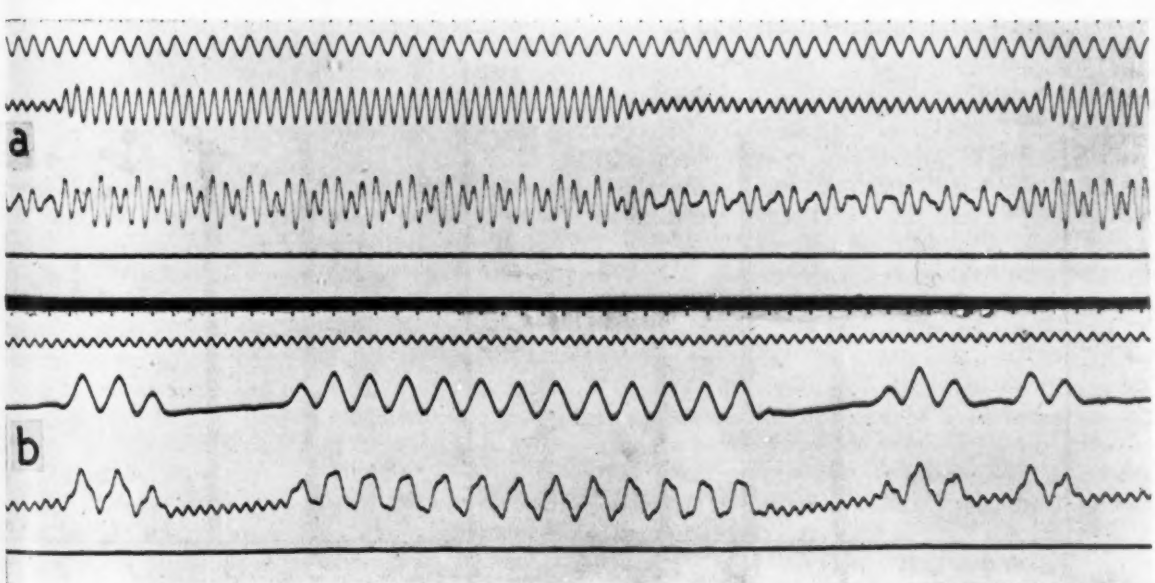

FIG. 4.—(*a*) Masking of a rhythm at 6 c./sec. by one of 8·5 c./sec. when the latter is the larger and the convers when the former is the larger; (*b*) Masking of a rhythm of slightly over 9 c./sec. by one of 3 c./sec. Note the progressive shift in phase relations indicated by the change in wave shape from square to triangular and back.

one rhythm by another. When the over-breathing response has developed, the 2–3 c./sec. waves are usually of considerably greater size than the rhythms in the resting e.e.g. The difficulty of measuring any faster rhythms, that have been present in the resting record, to see whether they have changed in size along with the development of the over-breathing response, is illustrated in Fig. 4 (*b*). In this record the component rhythms are, first a rhythm of 9 c./sec. of fixed amplitude and secondly, a paroxysmal rhythm at 3 c./sec., such as might occur in the e.e.g. as a result of over-breathing. During the periods when the 3 c./sec. waves are large the 9 c./sec. rhythm in the resultant may not be counted directly and the only indication of its presence is the deformation of the shape of the waves of the slower rhythm.

In the last record the masking of the faster by the slower rhythm is not due to beating, as has been described between rhythms of similar frequency, but is due to the harmonic relationship between the 3 c./sec. and the 9 c./sec. rhythms. This effect will be considered later together with the formation of specific wave-forms from harmonically related components.

The Analysis of Modulated and Beating Rhythms.—When a rhythm of frequency f_1 c./sec. is modulated at a frequency f_2 c./sec. it may be shown that the resulting modulated wave is exactly equivalent to the sum of three separate waves of frequency (f_1-f_2), f_1 and (f_1+f_2). Therefore, if analysis of a modulated wave, such as that shown in Fig. 3 (*a*), is plotted as a histogram it will show three components: 7·8 c./sec. (10−2·2), 10 c./sec., and 12·2 c./sec. (10+2·2), and will appear as in Fig. 5 (*a*). The characteristic of such an analysis is the equal size and symmetrical distribution about the rhythm f_1 of the two subsidiary rhythms (f_1-f_2) and (f_1+f_2), which are sometimes referred to as "side-bands." The chance of such a frequency and amplitude distribution occurring for three entirely independent rhythms is small.

When a fluctuating rhythm due to two separate rhythms beating together is analysed, and the components plotted in the same way as for the analysis of the modulated rhythm above, the result will be as shown in Fig. 5 (*b*). This result represents the analysis of the mixed rhythm of Fig. 3 (*d*) and shows no components other than those of equal size at 6 and 8·5 c./sec.

The difference between a modulated rhythm, which will show three components with a highly characteristic distribution, and a fluctuating rhythm due to beats, which will show only two components, is therefore made clear by this form of analysis.

Harmonic Series and Specific Waveforms.—The chief limitation of automatic e.e.g. analysis with instruments at present available lies in the fact that whilst they will separate and measure mixed and modulated rhythms in the e.e.g. they give no information about the relative phases of the waves making up these rhythms. When harmonically related higher frequencies are added to a fundamental frequency, the shape of the resulting waves depends entirely on the phase relations of the harmonics to the fundamental. Therefore, two compound waveforms which have components identical in frequency and size, and so will show the same analysis, may yet have entirely different shapes. In the visual examination of an e.e.g. record it is important to know some of the forms a given set of rhythms may produce by phase shifts of the components relative to one another. Such knowledge often makes it possible to deduce the presence in the e.e.g., without the aid of automatic analysis, of frequencies not directly countable.

A series of harmonically related components may produce an infinite variety of waveforms. Only

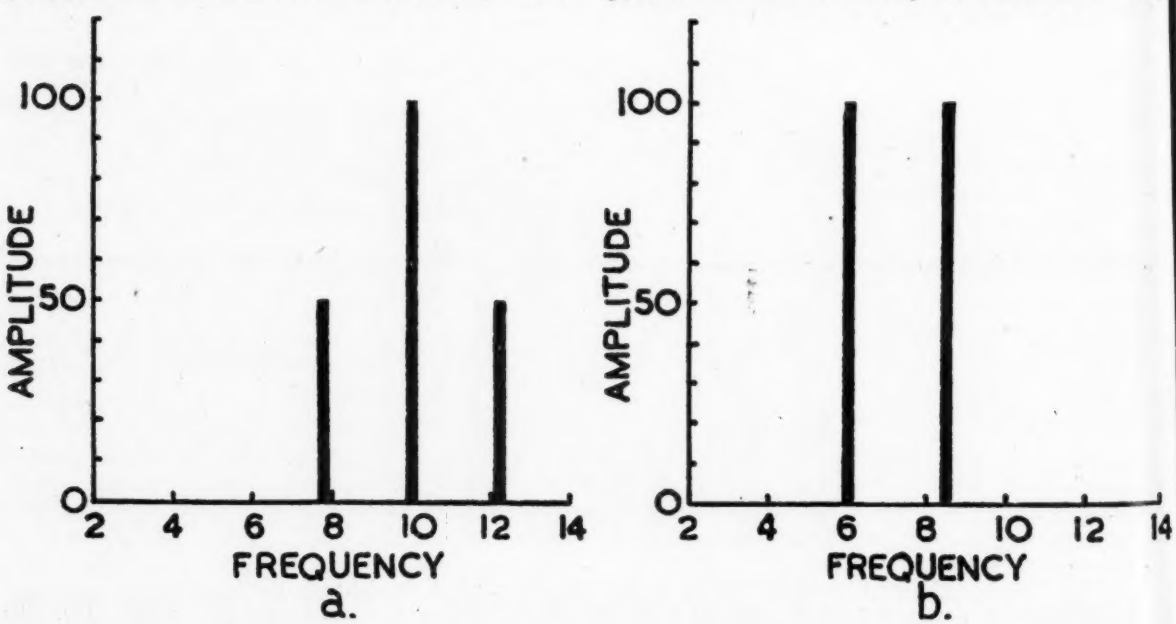

FIG. 5.—(*a*) Histogram showing components of Fig. 3 (*a*). (*b*) Histogram showing components of Fig. 3 (*d*).

certain shapes common in the e.e.g. need be considered here. How the shapes are built up may be seen most clearly from diagrams covering one cycle of the rhythm.

The first example to be given will be that of mixing two rhythms whose frequencies are in the ratio of 1 : 2, and where the size of the faster rhythm is one-half that of the slower rhythm. The result is shown for two conditions of phase relation; in Fig. 6 the second harmonic starts its first cycle in phase with the fundamental and in Fig. 7 it is advanced in phase by quarter of a cycle or 90°. Though the forms of the resultants are entirely different, their components and, therefore, their analyses are identical.

The combination of waves described above is a common one in the e.e.g. and is more noticeable in the flat topped form, for example, as an asymmetrical or " monophasic " alpha rhythm. In this case it contains components at about 10 c./sec. and 20 c./sec. It occurs also with a fundamental of 2·5–3 c./sec. in some epileptic conditions. Fig. 10 shows the appearance of this mixture of waves in the form of a continuous rhythm. In this figure the 10 c./sec. and 20 c./sec. rhythms are shown separately and then mixed together. The 20 c./sec. rhythm is about half as large as the fundamental, with which it is in phase. Fig. 11 shows the same components, but with the second harmonic retarded in phase by 90°. The fact that here the harmonic is retarded in phase causes the bottoms of the waves to be flattened, whereas when it is advanced in phase the tops became flattened, cf. Fig. 7.

The second example to be considered is that of adding to a fundamental rhythm another rhythm of three times its frequency. Fig. 8 shows the effect on the waveform of adding a third harmonic of 50 per cent. of the size of the fundamental and in phase with it at the beginning of the cycle. Fig. 9 shows the addition of the same waves in the same sizes, but with the harmonic advanced in phase by half a cycle or 180°. Here again the two resultants have the same components and analyses, but totally different shapes.

The difference between the wave of Fig. 6, due to the addition of second harmonic, and the wave of Fig. 9, due to the addition of third harmonic, should be noted. The former tends to become saw-toothed in shape as further harmonics are added and is steeper on one side of its peak than the other, while the latter becomes triangular but remains symmetrical on the two sides of its peak. In the same way the wave of Fig. 7 is asymmetrical above and below the baseline whilst that of Fig. 8 is symmetrical in this respect.

Fig. 12 shows, in the form of a continuous rhythm, the effect of adding to a fundamental rhythm of 10 c./sec. a third harmonic in phase with it: Fig. 13 shows the same addition but with the harmonic 180° out of phase. Here the contrast in waveform is very clear, as is the possibility of confusion between the waveforms of Fig. 10 and Fig. 13. When both second and third harmonics are added to a fundamental an even greater variety of waveforms is possible. Fig. 14 shows the effect of combining the waveforms of Fig. 10 and Fig. 13, the lower trace showing the resultant of the two harmonics alone. Here the extreme " spikiness " and the blur along the baseline are the noticeable features. Fig. 15 shows the same components, but as though Figs. 11 and 12 were combined. Here the waveform is quite asymmetrical about the baseline and the spikes are less sharp than in the other combinations. At the recording speed used the blur below the baseline due to the third harmonic is again visible.

If a faster rhythm is not an exact multiple of the frequency of a slower rhythm to which it is added the phase relations of the two rhythms will be constantly changing, and the form of the resultant will pass through the shapes illustrated in a cyclical manner. Thus the waves of Fig. 4 (*b*), due to mixing of a 3 c./sec. rhythm and one of not quite 9 c./sec., alternate between the flat-topped form of Fig. 8 and the triangular form of Fig. 9. This effect usually arises in the e.e.g. when the two rhythms that are mixing have some spatial difference in their origins. When the frequencies of two components are accurately locked together and keep constant phase relations it is usually found that no spatial differentiation of their origins can be made. When one of the rhythms drifts slightly in rate with respect to the other, as may be seen from the changes in the shapes of mixed rhythms, a difference in their places of origin should be sought.

Whenever the symmetrical flat-topped or triangular waveforms occur, the presence in the e.e.g. of rhythms at three times the frequency of the fundamental may be deduced. Such forms are common in the rhythms occurring in the e.e.g. in the presence of tumours. They indicate the presence, besides the easily counted 2, 2·5, or 3 c./sec. waves, of components at 6, 7·5, or 9 c./sec. respectively.

The third example to be shown is the waveform produced when two rhythms with frequencies in the ratio of 2 : 3 are mixed in equal size. Fig. 16 shows two rhythms compounded from these components: (*a*) in phase, and (*b*) with the 3 c./sec. rhythm advanced in phase by 90° on the 2 c./sec. rhythm. It will be noticed that the effect of a phase shift on the wave form is much less marked than when the frequencies are more widely separated. Also a periodic fluctuation in the size of the wave is beginning to show every other wave. The critical frequency difference at which the eye begins fully to appreciate the presence of beats seems to lie at about a ratio of frequency of 4 : 3. Fig. 17 shows this effect. Here two rhythms with a constant difference of 1 c./sec. are shown and the frequencies are progressively reduced from 7 and 6 to 2 and 1 c./sec.

A striking example of the changes in form that may result from a change in the phase relations of the components of a wave, with their size remaining constant, is given by the synthetic waves of Fig. 18. The basis of the synthesis is an analysis of a wave

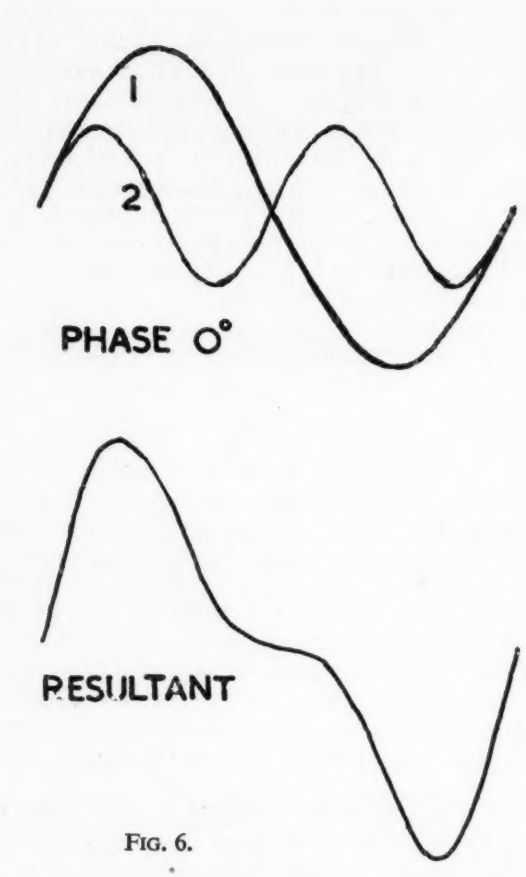

FIG. 6.

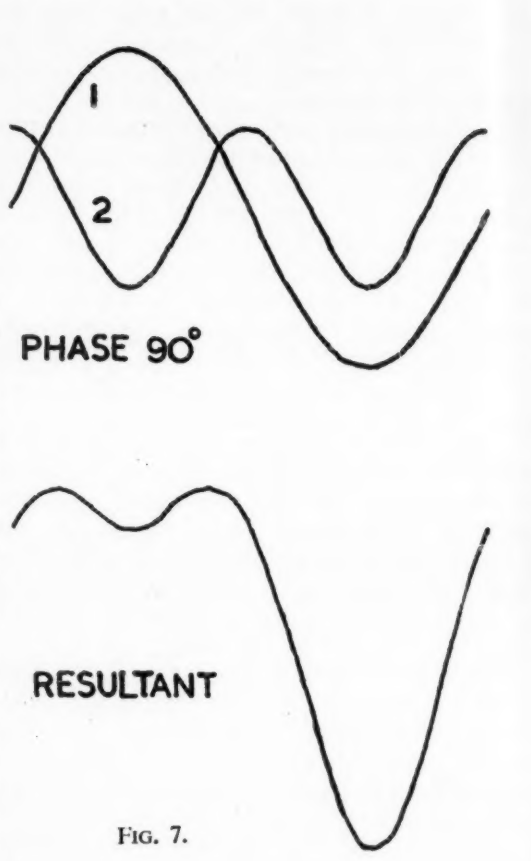

FIG. 7.

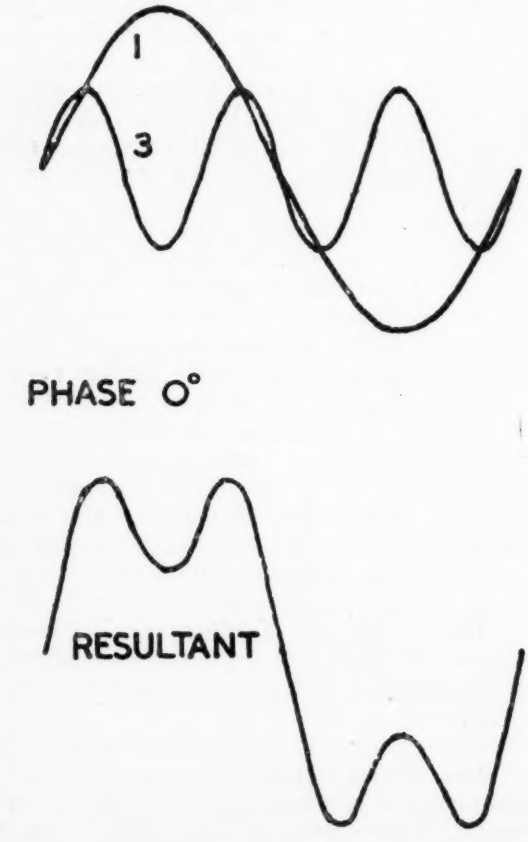

FIG. 8.

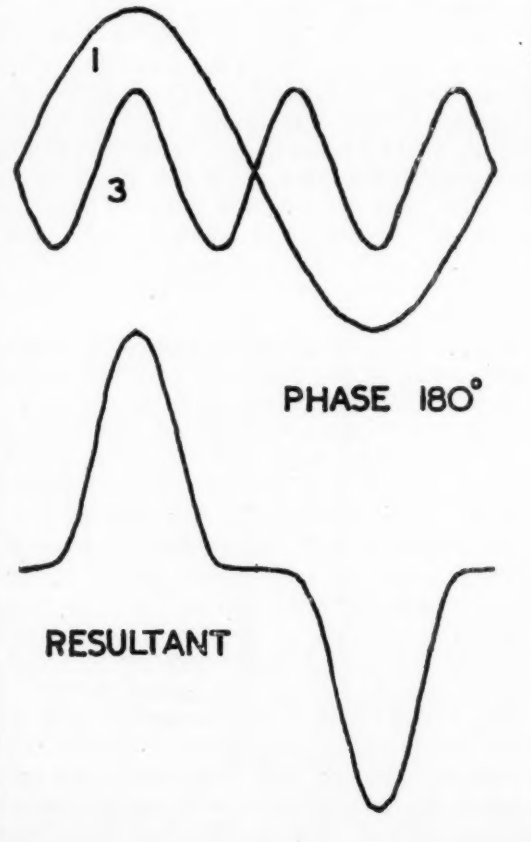

FIG 9.

FIGS. to 6 9.—Graphs showing combination of fundamental with its second and third harmonic. Explanation in text.

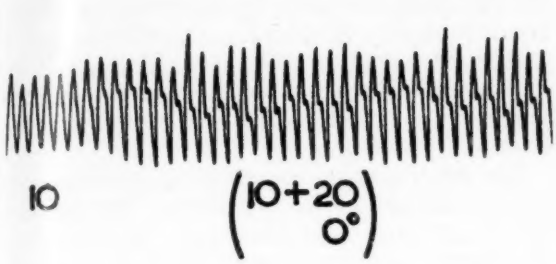

FIG. 10.

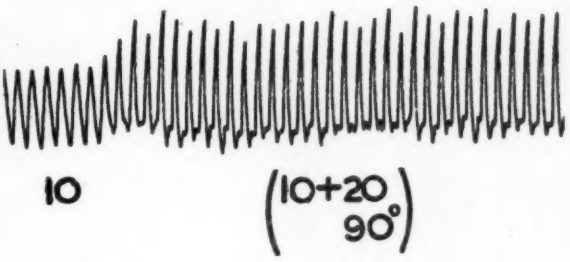

FIG. 11.

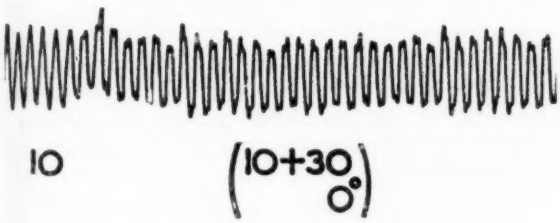

FIG. 12.

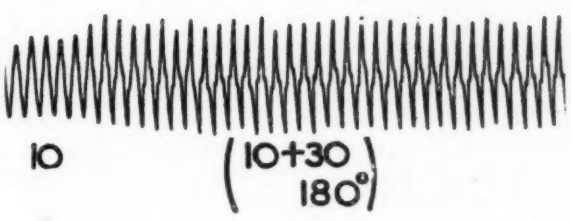

FIG. 13.

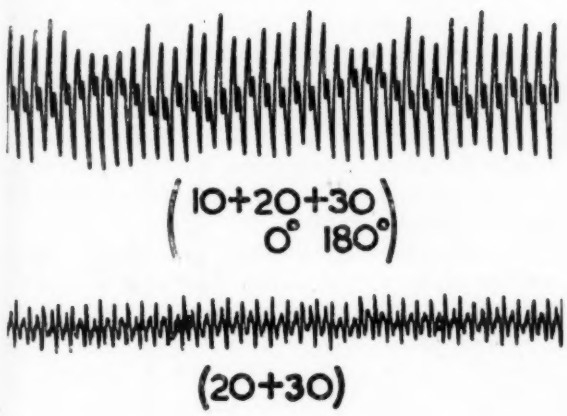

FIG. 14.

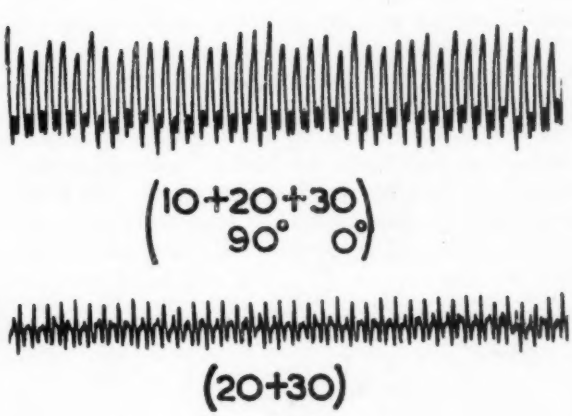

FIG. 15.

FIGS. 10 to 15.—Ink-oscillograph tracings of rhythms at 10, 20, and 30 c./sec. with various phase relations. The numbers refer to the frequencies present in the trace above and the phase relation of the harmonic to the fundamental in degrees.

and spike discharge from an epileptic subject. The components in the sizes and frequencies indicated in this analysis have been mixed together. Fig. 18 shows first, the spike form produced by the addition of nine frequencies in the ratios of 2, 3, 4, 5, 6, 7, 8, 9, and 10, all in phase; secondly, how the addition of the fundamental frequency 180° out of phase with the other components results in the characteristic wave and spike formation. This arrangement of amplitudes, frequencies, and phases results in the formation of a single spike at the fundamental frequency. Fig. 18 (*b*) shows the same components as those responsible for the wave and spike, but out of phase so that although a pattern is produced which repeats at the fundamental frequency, no single spike occurs, and the outline appears more complex. Between the arrows the phase relations of the components are varied at

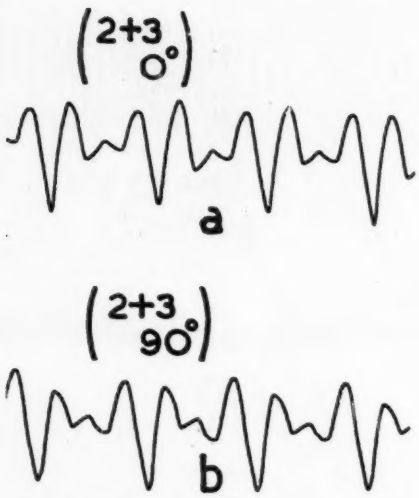

FIG. 16.—(*a*) Combination of a rhythm at 2 c./sec. with one at 3 c./sec. in phase. (*b*) The same 90 degrees out of phase.

random and their amplitudes held constant. The waveform here is even more confused and resembles more closely a type of record actually obtained in an epileptic patient between seizures. Fig. 18 (*c*) shows the added complexity developed when both phase and amplitude are randomized. Again the resemblance to a natural e.e.g. is even more obvious.

The above examples should make clear the important relation between phase and waveform in complex rhythms. Since instruments for automatic analysis of such rhythms give no information about phase relations, the closest possible association should be maintained between the result of an analysis and the primary record to which it applies.

The value of a wave synthesizer for checking analyses, as well as for demonstration and instruction, is quite considerable.

Separation of Rhythms by Examination Technique.—When an automatic method of analysis is not available it becomes necessary to get the best from every other possible method of separating the components of a complex record. If there are several rhythms occurring in a record and all appear in exactly the same place on the scalp, or in places so close together as to be inseparable by recording from the scalp, separation by examination techniques is not possible. If, however, the rhythms arise in slightly or widely different parts of the brain and appear separable to even a small extent on the scalp, much may be done to simplify the record by suitable electrode placements.

The importance of close electrode placements and bipolar leading for giving the simplest possible record was emphasized by Adrian and Matthews (1934) and Adrian and Yamagiwa (1935). The principle to be used for separating mixed rhythms by electrode placing may best be presented by considering the case, already mentioned, of a parieto-occipital 4–7 c./sec. rhythm and an occipital alpha rhythm.

If the potential gradients produced by the alpha rhythm are plotted, it will be found that they run roughly from the occipital region to the frontal and temporal regions. It is therefore possible to plot out a series of lines at right angles to the radiating gradient lines, such that the points along these lines will have no differences of potential. The gradient lines for a typical alpha rhythm are shown in Fig. 19 (*a*), and the equipotential lines corresponding to them in Fig. 19 (*b*). If now electrodes placed along the line R, roughly from ear to ear, are used for bipolar recording, the alpha rhythm will either disappear altogether from the record or will be reduced so much that the forms of any other rhythms will not be confused. The 4–7 c./sec. rhythms given as an example usually have an appreciable potential gradient between the parietal and the temporal regions, and so appear unreduced in size with this electrode placement.

The principle of placing electrodes to reduce the size in which particular rhythms will appear in the record may be employed in any part of the head, once the approximate distribution has been worked out for the potential differences against which it is wished to discriminate. It is particularly valuable where the effect of attention, and of opening and closing the eyes, on rhythms other than the alpha rhythm, is to be studied.

An example of the manner in which the suitable placing of electrodes makes it possible partially to separate a complex rhythm into its components is shown in Fig. 20 (*a*). The record is of a wave and

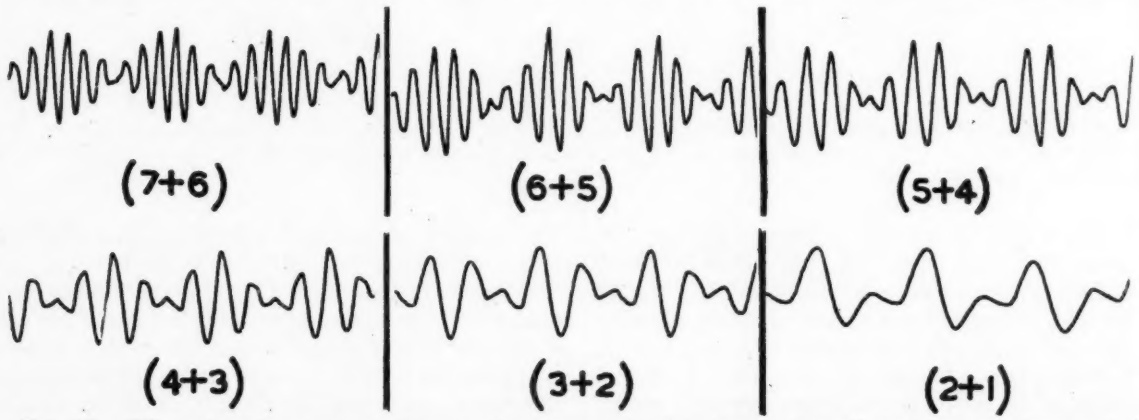

FIG. 17.—Change in the appearance from beats to harmonic distortion as the ratio between two frequencies is increased.

FIG. 18.—(*a*) Synthesis of wave and spike rhythm by addition of 10 sinusoidal components in correct phase relations. (*b*) The same components with phase relations disturbed and randomized. (*c*) The same components with both phase and amplitude randomized.

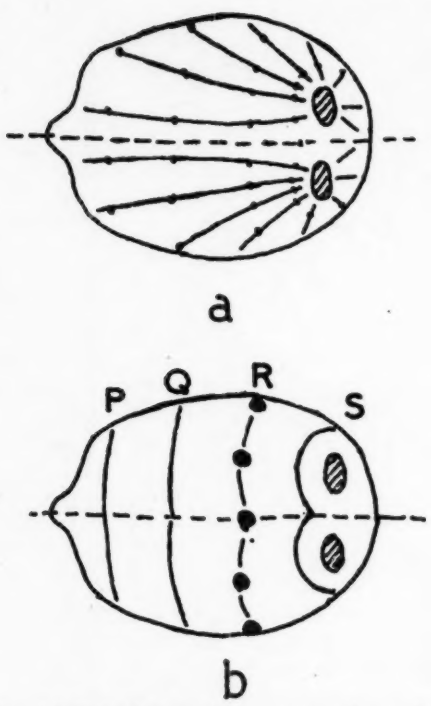

FIG. 19.—(*a*) Potential gradients across the scalp due to two alpha rhythm foci in the occiput. (*b*) Equipotential lines derived from above.

spike seizure in a subject in whom it is possible to predict accurately the distribution of potential that will occur during such an attack. With the electrodes arranged as shown in the figure the two electrodes of channel three, R and S, are on an equipotential line with respect to the wave, which therefore practically disappears, but the spike is not reduced in size and therefore has a potential distribution different from that of the wave. Also it is possible to say that, between the second and third, and third and fourth waves of the seizure, the origin of the spike has shifted from below electrode S to below electrode R and back again, without any corresponding change in the distribution of potential of the wave.

Discussion

The electroencephalogram is essentially a graph of changes of potential difference with respect to time; in common with any other such graph the waveforms that occur will obey well defined physical principles. The examples of mixed rhythms that are given seem to show quite clearly that in many cases it is not possible to count directly some of the component rhythms. In some cases the importance of component rhythms that are often masked has been demonstrated (Walter and Dovey, 1944), but in others the significance of changes in the masked components has not yet been assessed. If these waves are to be used either as an aid to the distinguishing of abnormality, or in investigation of physiological changes in the e.e.g., every possible means must be used to separate them from the masking rhythms.

When a method of full automatic analysis is not available the first step to be taken should be to obtain as simple a record as is possible. The use of closely spaced bipolar electrodes is of value here as, when two rhythms have spatially different origins, it is possible to discriminate against a large rhythm, and so leave clear for investigation a smaller rhythm it is masking. When the rhythms are not separable by this means the presence of masked rhythms may often be deduced from the forms of the compound rhythm. This method, although it allows the presence of rhythms not directly countable to be described, is of little value as a means of measuring the size of masked rhythms.

Visual examination of an e.e.g. record and direct measurement of the waves in it is reliable so long as the rhythms under investigation are significantly larger than any others present. When, however, the rhythm which is being studied becomes comparable in size with, or smaller than others which are present, a visual examination of the record may be completely misleading unless the masking rhythm can be reduced in size in the record, or some specific shapes occur. For example, in the assessment of the effect of physiological factors on the response of the e.e.g. to over-breathing, any slow waves that may be produced will become countable and measureable as soon as they significantly exceed in size any other rhythms that are present. As soon as this occurs, however, any further changes that may take place in the smaller rhythms will be masked and may not be assessed; Fig. 4 (*b*).

If any significance is to be found in changes in rhythms that are masked, either for reasons of size or because of their harmonic relationship to slower rhythms, some form of automatic analysis of the e.e.g. must be used.

In analysing an irregular waveform, such as that of the e.e.g., the record has to be divided up into arbitrary sections corresponding to periods of time. A transient outburst in the e.e.g. may fail to appear significantly in analysis if the duration of the outburst is short in comparison with the length of time chosen for the analysis. The appearance of such an outburst may be highly characteristic and have great significance in interpretation. This is therefore one of the limitations of automatic analysis. The other limitation is the inability of the method to express the phase relations of the components of a compound rhythm.

The importance of the phase relations of the components in a complex wave has been shown in the simple cases of the waves formed from a fundamental and one or two harmonics, and also for the more complicated case of the wave and spike discharge. When a number of rhythms are associated together in a complex wave, and keep constant phase relations, the question arises as to whether or not the components shown in an analysis have any separate existence apart from the fundamental rhythm.

In the case of a fluctuating rhythm, due to two independent rhythms beating together, it is seen that the analysis shows nothing but the two rhythms

FIG. 20.—(*a*) Cathode-ray oscillograph record from a patient with Petit Mal showing wave and spike formation and spatial separation of "wave" and "spike" components. (*b*) Synthetic wave and spike showing successive subtraction of the ten components. (*c*) Synthetic wave and spike showing successive addition of the ten components.

concerned. As the two waves are usually found to have spatially different origins, their appearance in the analysis as two separate components is obviously a correct presentation of the mode of production of the compound wave. The rhythms may therefore be considered as real components that have separate existences. In the case of the modulated rhythm, which shows in analysis three components, the important question to answer is whether these components can be spatially separated or not. If this is not possible by any means whatever, then it seems more likely that the modulation is produced by a fluctuation in the excitability, or degree of synchronization, of a group of cells producing the rhythm, rather than by an exact locking together in the correct ratios of frequency, size, and phase relation of the oscillations of three separate groups of cells. When the three rhythms can be separated spatially, the appearance of modulation is attributable to the existence of three components as distinct entities, and careful location technique will display the components with relatively constant amplitudes.

The possible ambiguity of a three-component analysis illustrates again the essentially complementary relation between the primary records and analyses. In the case where a component in an analysis cannot be shown to have a distinct existence in the primary record, and when there is reason to believe that the component is a modulation product, such a component may be referred to as imaginary.

Where a complex wave shows, in analysis, a fundamental and several harmonics, again some test must be applied to decide whether the harmonics are real or imaginary components. If the harmonically related frequencies cannot be shown to have a separate origin, and their frequencies remain at all times exact multiples of that of the fundamental, it seems likely that the deformation of the wave from the simple sine form is taking place as a result of some inherent limitation in the amplitude with which the group of cells producing it may oscillate. The components will then have no separate existence apart from the fundamental and may be considered as imaginary. When, however, it may be shown that either the harmonics have a different site of origin, even though this difference may be small, or that they do not keep an exact harmonic relation to the fundamental and drift slowly in phase, producing cyclical changes in the form of the compound wave, then it seems justifiable to consider them as being real components and having separate existences.

The question as to what part is played by real and imaginary components becomes of great importance in considering the mode of formation of a complex rhythm, such as that of the wave and spike. Analysis of records from patients liable to wave and spike seizures shows that even between their seizures the component frequencies of the wave and spike discharge are often present in considerable size (Walter, unpublished observations). This observation may suggest that at the time of the seizure a number of separately oscillating systems, which at rest have random phase relations, are becoming locked together in some way to produce the wave and spike discharge. If this is so it implies that some at least of the components in the analysis of the wave and spike rhythm are real and not imaginary. The record shown in Fig. 20 (*a*) of a wave and spike rhythm, showing that the spike and the wave may have different potential distributions on the scalp, supports the idea of separately oscillating systems. The spike itself is a complex wave with a large number of components and the record shows the presence of several of these components when the spike has lost its characteristic form at the point marked by the arrow in Fig. 20 (*a*). This should be compared with the analogous point similarly marked in the synthetic record in Fig. 20 (*b*). In this record the components of the synthetic spike and wave rhythm have been subtracted one by one until, when only the frequencies in the ratio 6, 7, 8, 9, and 10 remain, the resultant is a periodic wave group without characteristic form. Similarly, Fig. 20 (*c*) shows how the progressive addition of the constituent frequencies brings about a closer and closer resemblance to the wave and spike formation. Therefore, though some of the components of the wave and spike analysis may be imaginary, others, such as those marked by the arrow in Fig. 20 (*a*), may be shown to have a spatial difference from the fundamental and are certainly real. The question of how the outbursts of frank wave and spike arise is still an open one, but the value of a full automatic analysis of the e.e.g. potentials in investigating this and other problems should be clear.

Summary

1. The complex nature of the waves recorded in the e.e.g. is considered.

2. The use of a synthetic method for demonstrating the formation of complex waves, such as occur in the e.e.g., is described.

3. Mixed rhythms of types common in the e.e.g. are synthesized, and the effects on the form of such rhythms of variations in the size and frequency of their components is demonstrated.

4. Certain types of waves which have entirely different compositions are shown to be indistinguishable to the eye.

5. The specific forms that are produced when certain common harmonically related components are added together are shown.

6. The effects on the above forms of the phase relations of the components are demonstrated.

7. The use of the specific forms as a basis for deducing the presence in the e.e.g. of rhythms not obvious to the eye is indicated.

8. Simplification of the e.e.g. by the use of close bipolar leads is suggested.

9. It is suggested that many of the complex e.e.g. waveforms are due to the simultaneous generation of a number of harmonically related sinusoidal waves.

10. The application of the principles described to e.e.g. examination both with and without automatic analysis is discussed, and the limitations and

possibilities of visual and automatic analysis of the e.e.g. are considered.

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References

Adrian, E. D., and Matthews, B. H. C. (1934). *J. Physiol.*, **81,** 440.
—, and Yamagiwa, K. (1935). *Brain*, **58,** 323.
Davis, H., Davis, P. A., Loomis, A. L., Harvey, E. N., and Hobart, G. (1938). *J. Neurophysiol.*, **1,**, 24.
Drohocki, Z. (1938). *Comptes Rendus Soc. Biol.*, **129,** 889.
Gasser, H. A., and Erlanger, J. (1927). *Amer. J. Physiol.*, **80,** 522.
Grass, A. M., and Gibbs, F. A. (1938). *J. Neurophysiol.*, **1,** 521.
Kurtz, E. B., and Larsen, M. J. (1935). *Elect. Eng.*, **54,** 950.
Livanov, M. M., and Petrova, N. G. (1938). *Med. Experimentale* (*Ukraine*), **2,** 31.
Parr, G., and Walter, W. G. (1943). *J.I.E.E.*, **90,** Part 3, 129.
Rohracher, H. (1937). *Pflügers Archiv.*, **238,** 535.
Schaffer, W., and Lubsynski, G. (1931). *Proc. Inst. Radio Eng.*, **19,** 1242.
Somerville, J. M. (1944). *J. Sci. Instr.*, **21,** 174.
Walter, W. G. (1943*a*). *Electronic Engineering*, **16,** 9.
—— (1943*b*). *Ibid.*, **16,** 236.
—— and Baldock, G. R. (1944). *Ibid.* In press.
—— and Dovey, V. J. (1944). *J. Neurol. Neurosurg. Psychiat.*, **7,** 57.

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